Journal of Diabetes Science and Technology
Volume 3, Issue 4, July 2009

SYMPOSIUM

Arguments for and against the Role of Glucose Variability in the Development of Diabetes Complications

Eric S. Kilpatrick, M.D.

Abstract

There is now unequivocal evidence that improving glycemic control in both type 1 and type 2 diabetes reduces the likelihood of developing the micro- and macrovascular complications of the disease. However, it is still unclear whether a patient with very variable glucose is at any different a risk of these problems than someone who has the same mean glucose but much more stable glycemia. This article reviews the evidence that exists to both support and refute the claim that increased glucose variability should be regarded as an independent risk factor for the development of diabetic vascular disease.

J Diabetes Sci Technol 2009;3(4):649-655

Introduction

Over the past two decades the measurement of glycated hemoglobin (HbA1c) has become central to the glycemic management of patients with diabetes. Having determined that hemoglobin A1c could be used as a surrogate marker for the average glucose of a patient with diabetes,[1] the Diabetes Control and Complications Trial (DCCT) in type 1 and the United Kingdom Prospective Diabetes Study (UKPDS) in type 2 diabetes demonstrated an exponential relationship between rising blood glucose (BG) and the risk of either developing or worsening retinopathy, nephropathy, and neuropathy.[2,3] More recently, the long-term follow-up study of the DCCT cohort, the Epidemiology of Diabetes Interventions and Complications (EDIC) study, found that intensive treatment during just the period of the DCCT markedly reduced the long-term risk of cardiovascular disease by 42%, with differences in HbA1c between treatment groups (rather than simply changes in known cardiovascular risk factors) accounting for much of the benefit.[4] Likewise, the 10-year follow-up of patients in the UKPDS has found a clear reduction of about 15% in both myocardial infarction and death from any cause among subjects who were treated intensively during the original period of that study.[5]

Author Affiliation: Department of Clinical Biochemistry, Hull Royal Infirmary, Hull, United Kingdom

Abbreviations: (BG) blood glucose, (CV) cardiovascular, (DCCT) Diabetes Control and Complications Trial, (EDIC) Epidemiology of Diabetes Interventions and Complications, (HbA1c) glycated hemoglobin A1c, (HEART2D) Hyperglycemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients With Type 2 Diabetes, (IFG) impaired fasting glucose, (IGT) impaired glucose tolerance, (8-iso-PGF2α) 8-iso-prostaglandin F_2, (MAGE) mean amplitude of glycemic excursion, (PPG) postprandial glucose, (SD) standard deviation, (UKPDS) United Kingdom Prospective Diabetes Study

Keywords: complications, diabetes, glucose variability, glycated hemoglobin

Corresponding Author: Prof. Eric S. Kilpatrick, M.D., Department of Clinical Biochemistry, Hull Royal Infirmary, Anlaby Road, Hull HU3 2JZ, United Kingdom; email address Eric.Kilpatrick@hey.nhs.uk

Understandably, these trials have focused attention on using HbA1c as a marker of glycemia and shown the benefit of reducing average glucose to near normal in subjects with diabetes. Yet despite these findings, the DCCT investigators observed that "total glycemic exposure" (HbA1c and duration of diabetes) explained only about 11% of the variation in retinopathy risk in the complete DCCT cohort, meaning that factors independent of HbA1c must presumably explain the remaining 89%.[6] Among proposed factors, such as a genetic predisposition to complications, it has been suggested that glucose instability around an individual's mean value may be one of these other explanatory variables, such that increased glucose variability would place a patient at especially high risk.[7]

A recent "symposium" paper in this journal described in detail how glucose variability can influence the risk of hypoglycemia.[8] This article aims to explore the arguments which either support or refute the suggestion that increased glycemic instability around a given mean glucose will add to the risk of either micro- or macrovascular complications in patients with diabetes.

What Is Glucose Variability and How Should It Be Described?

This first part of this question is not as straightforward to answer as would seem to be the case initially. For most people, the term "glucose variability" would describe the hour-to-hour within-day fluctuations in blood glucose that a person with diabetes experiences. However, marked changes in blood glucose can also exist over longer periods of time (day to day, week to week, and month to month), which cannot be regarded as anything but variability as well. Even within-day instability can either be due to the effect of mealtimes on blood glucose, representing pre- and postprandial changes, or may be unrelated to food. This distinction is of relevance because postprandial changes in blood glucose have, in particular, been implicated with an increased risk of developing macrovascular complications.

How to assess glucose variability is no less simple to describe either. The most mathematically familiar assessment is that of the standard deviation (SD) of the glucose profile. However, SD is limited by being unable to identify (or weight) the marked peaks and troughs that may be causing patients their largest problems, especially where hypoglycemia is concerned. As a consequence, various other measures of instability have been proposed. One of the most venerable is that of mean amplitude of glycemic excursion (MAGE), which was suggested in 1970 as a more appropriate means of detecting significant swings in glycemia.[9] Since then, there have been, among others, the average daily risk range used to assess a composite of high and low glucose extremes,[10,11] the Glycaemic Risk Assessment Diabetes Equation[12] with a similar remit, and separate low BG and high BG indices.[13,14] This absence of a single definition for glucose fluctuations has meant that it has either become very difficult to compare studies (simply because the methodology of assessment is often quite different) or that interpretation of analyses has become unwieldy because all measures have been tried and used.

The way in which glucose is measured in order to assess instability has also changed in recent years. Outside of a clinical trial, this has traditionally taken the form of pre- and postprandial glucose measurements using glucose test strips. Continuous glucose monitoring has become more widespread, providing the opportunity to establish a more accurate assessment of glucose fluctuation.

The Case 'for' a Relationship between Glucose Variability and Complication Risk

Glucose Variability and the Formation of Reactive Oxygen Species

Michael Brownlee's unifying mechanism for diabetes complications is both elegant and compelling. He described how the development of all diabetes complications could ultimately be explained by overproduction of the reactive free radical molecule, superoxide, generated in response to hyperglycemia acting on cellular mitochondria.[15]

Several studies have found that glucose instability can cause a marked rise in the formation of markers of free radical damage. Perhaps the one that has had greatest recent impact is the work by Monnier and colleagues,[16] which measured the production of the urinary isoprostane 8-iso-prostaglandin F_2 (8-iso-PGF2α), a recognized marker of oxidative stress, in 21 patients with type 2 diabetes. They found that isoprostane production was not so much influenced by the average glucose of their patients, but instead was more closely associated with their glycemic variability as assessed by MAGE. In concert with Brownlee's hypothesis, it provided circumstantial evidence that glycemic excursions could influence the development of diabetes complications.

Ceriello's group has published widely on data supporting the concept that intermittent hyperglycemia can influence various other markers of oxidative stress,[17–20] both in cell culture and in human subjects. By doing so, this may go some way toward explaining the observation known as "metabolic memory," where glycemia early in the diabetes disease appears to be "remembered" so far as complications are concerned.[21]

Glucose Variability and HbA1c

Monnier and colleagues[22,23] have also been instrumental in quantifying the relative contributions of pre- and postprandial hyperglycemia toward the HbA1c of patients with type 2 diabetes. They found that as HbA1c worsens from nondiabetic values it is initially mainly as a consequence of postprandial hyperglycemia, while it is only at an HbA1c in excess of 8–9% that the preprandial glucose concentrations become the dominant contributor.[22,23] This predominance of postprandial hyperglycemia at lower HbA1c means that these type 2 subjects are likely to have glycemic fluctuations comparable to patients who are much more poorly controlled. If glucose variability does indeed have an influence on complication risk, it infers that even relatively well-controlled type 2 patients could still be prone to developing problems.

Glucose Variability and Microvascular Complications

One of the main reasons for pursuing the possibility of glycemic instability as a risk factor for microvascular complications arose from one of the original analyses of the DCCT data set.[24] It found that the rate of complications at a given value of HbA1c was apparently higher in the conventionally treated patients in the trial than in those treated intensively. The magnitude of this difference was such that a conventionally treated patient with an HbA1c of 8% had at least the same risk of retinopathy as a patient with an HbA1c of 9% treated intensively. This led to the suggestion that the discrepancy could be a consequence of larger glycemic excursions in the former group of patients as they were on fewer injections of insulin per day.[7]

Also in support of this was an observational report where the incidence of retinopathy in a group of adolescents with type 1 diabetes appeared to fall substantially between 1990 and 2002, despite HbA1c levels changing little throughout the study period.[25] It was again speculated that the transition to multiple injection regimes over the time period may have contributed to this improvement by reducing glycemic fluctuations rather than mean glucose.

Another study has assessed variability in fasting glucose at the same HbA1c and found this to independently predict retinopathy development among 130 patients with type 2 diabetes,[26] and more recently the SD of blood glucose has been found to independently predict neuropathy in 100 individuals with type 1 diabetes.[27]

Returning to the DCCT, a reanalysis of the database found that variability in HbA1c (rather than glucose) added to that of average HbA1c in predicting microvascular risk,[28] suggesting that longer term changes in glycemia may also be of relevance to complication development.

Glucose Variability and Macrovascular Risk

When discussing any influence that glucose variability may exert on the risk of large vessel disease it is impossible to avoid the topic of postprandial hyperglycemia, which is, after all, a major contributor to overall variability.

Numerous studies have shown that postprandial glucose (PPG) is predictive of future cardiovascular events, although most data are in subjects not already diagnosed as having diabetes.[29–32] Among patients with type 2 diabetes, evidence still exists that postprandial glucose peaks correlate with carotid intimal thickness,[33] as well as the harder end point of cardiovascular events.[34,35]

Crucially, reducing PPG seems to be of benefit and perhaps preferentially compared with reducing preprandial glucose alone. Carotid intimal thickness regression was found to be much more frequent in 88 type 2 patients treated with repaglinide (which reduces postprandial glucose) than in the 87 patients given glyburide, despite both groups showing identical reductions in HbA1c.[36] Powerful evidence that reducing PPG also reduces cardiovascular (CV) events has come from the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus trial, which used the α-glucosidase inhibitor acarbose to specifically lower postprandial glycemic excursions in subjects with impaired glucose tolerance.[37] As well as reducing the progression to diabetes, there was also a marked 49% reduction in cardiovascular events among those of the 1368 individuals placed on active treatment rather than placebo over an average time period of just 3.3 years.

Little evidence currently exists on any association between glucose variability and the CV risk of patients with type 1 diabetes.

The Case "against" a Relationship between Glucose Variability and Complication Risk

Glucose Variability and Formation of Reactive Oxygen Species

Not every study has shown that glycemic instability is certain to lead to an increase in markers of free radical damage. In contrast to the study by Monnier *et al.*, which showed a close relationship between glucose variability in type 2 diabetic patients and their urinary excretion of 8-iso-PGF2α, de Vries' group has shown no such association in type 1 diabetes. This was despite using a similar methodology but with more participants, a wider range of glucose variability, and employing a more specific method to measure the isoprostanes.[38]

Glucose Variability and HbA1c

Because HbA1c is a good predictor of microvascular complications, then it is only natural to enquire whether two patients with the same mean blood glucose but very different glucose variability will have similar HbA1c values. Three main studies have addressed this question (one using DCCT data) and found that glucose instability seems to have little influence on the HbA1c result; rather the mean glucose appears to be the main determinant, no matter how the mean is arrived at.[39,41] This also suggests that neither pre- or postprandial hyperglycemia has a preferential influence on the HbA1c result.

Glucose Variability and Microvascular Complications

The DCCT data set has been analyzed to determine if the seven-point laboratory-measured glucose day profiles, determined quarterly, could give further insight into any role played by glycemic instability in the development of small vessel complications. While with univariate analysis there did indeed seem to be an association between glucose fluctuations and both retinopathy and nephropathy risk, this was due to the fact that patients with the most variable glucose were also those with the highest mean values. Taking this into account in a multiple regression model, only the mean glucose, not its instability, predicted the risk of these two complications.[42] DCCT data have not been examined to see if neuropathy is related to variability.

Looked at more closely, the DCCT also showed no preference for pre- or postprandial hyperglycemia in the development of retinopathy or nephropathy, although it must be said that the postprandial rises in type 1 diabetes may not be directly comparable to those found in patients with type 2 diabetes who are not taking insulin or oral agents.

The conclusions of these DCCT data analyses were at odds with the 1995 DCCT group publication described in the "for" section of this article.[24] It suggested more complications at the same HbA1c among conventionally treated patients, presumably as a consequence of more glycemic variability. Two more recent papers have helped reconcile the situation by showing (1) that conventionally treated patients actually had higher blood glucose values than intensively treated ones at the same HbA1c[43] and (2) that differences found between treatment groups were probably artifacts of model assumptions originally used.[6]

The UKPDS only assessed fasting glucose values rather than the seven-point profiles of the DCCT, but the fact that insulin (where patients are liable to greater glycemic instability) did not seem to confer a higher risk of microvascular disease than oral hypoglycemic agents makes a positive association in type 2 diabetes less likely.[3]

Glucose Variability and Macrovascular Risk

Recent studies have not been able to replicate most earlier ones showing that postprandial hyperglycemia is more of a cardiovascular risk than preprandial hyperglycemia. For example, among the 6888 participants with no known diabetes or CV disease in the Atherosclerosis Risk in Communities study, the presence of impaired glucose tolerance (IGT) did not seem to predict coronary events any differently than that of impaired fasting glucose (IFG).[44] Among the 10,428 Australian Diabetes, Obesity, and Lifestyle Study participants it was actually IFG that seemed to be predictive of CV mortality when IGT was not.[45]

The main intervention study specifically targeting postprandial hyperglycemia (and therefore reducing glucose variability) in patients with diabetes has also shown no benefit. Results from the Hyperglycemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients With Type 2 Diabetes (HEART2D) study were reported at the American Diabetes Association conference in June 2008. Patients in this study were enrolled within 3 weeks of a myocardial infarction to receive either a prandial or a basal insulin strategy with a view to establishing if the targeting of postprandial hyperglycemia preferentially

reduced the incidence of further cardiovascular events. The study was apparently successful in achieving two groups of patients with the same mean HbA1c of 7.6%, but this was attained with very different glucose profiles. However, this did not translate into any differences in the number of cardiovascular outcomes, with 181 events in the prandial and 174 in the basal insulin groups.

In retrospect, given the difficulty that other larger studies, such as the Action to Control Cardiovascular Risk in Diabetes,[46] Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation,[47] and Veterans Affairs Diabetes Trial,[48] have experienced in showing that actually improving glycemic control from this level of HbA1c can lead to any significant improvement in macrovascular complications, it is perhaps not surprising that HEART2D did not show reduced risk among patients whose sole difference was the way in which they achieved the same HbA1c.

Even the DCCT and UKPDS struggled to show any cardiovascular benefits to intensive treatment of hyperglycemia, with both studies showing trends toward improvement but failing to reach statistical significance. This was also despite patients starting with higher HbA1c values than in most of the recent studies just stated. As mentioned earlier, it was only with prolonged follow-up of these patients (in the EDIC study[4] and the 10-year follow-up of the UKPDS[5]) that the macrovascular advantage conferred by intensive glucose treatment became obviously apparent. Consequently, it may be that studies similar to HEART2D would need to be conducted over a much longer period of time—and possibly in patients earlier in the stage of their diabetes and cardiovascular diseases—before any improvement has a hope of being shown.

Finally, another analysis of DCCT data has shown that while mean HbA1c was not predictive of cardiovascular events during the original study, mean blood glucose was.[49] Again, as with microvascular complications, the glucose variability of patients did not seem to add to the risk already forecast from the mean glucose alone.

Conclusion

The precise role of glucose variability in the development of vascular complications is now one of the largest remaining unanswered questions in diabetes. This article showed that currently the situation remains unresolved. The challenge to proponents remains the ability to clearly demonstrate that glycemic variability worsens the vascular prognosis for a patient over and above that already predicted by their mean glucose. Perhaps more importantly, it is also to know if an intervention to reduce instability will reduce any excess risk. In reality, it may be easier to show the latter rather than demonstrate the former, as many of the new drug classes emerging specifically target postprandial excursions,[50] thereby reducing glucose fluctuations. It is hoped that forthcoming trials with these new agents will, either by fortune or by design, be able to show whether the benefit of glycemic stability extends beyond that of reducing hypoglycemia.

References:

1. The Diabetes Control and Complications Trial Research Group. Diabetes Control and Complications Trial (DCCT): results of feasibility study. Diabetes Care. 1987;10(1):1-19.
2. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329(14):977-86.
3. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352(9131):837-53.
4. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med. 2005;353(25):2643-53.
5. Holman R, Paul S, Bethel M, Matthews D, Neil H. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359(15):1577.
6. Lachin JM, Genuth S, Nathan DM, Zinman B, Rutledge BN; DCCT/EDIC Research Group. The effect of glycemic exposure on the risk of microvascular complications in the diabetes control and complications trial--revisited. Diabetes. 2008;57(4):995-1001.
7. Hirsch IB, Brownlee M. Should minimal blood glucose variability become the gold standard of glycemic control? J Diabetes Complications. 2005;19(3):178-81.
8. McCall AL, Kovatchev BP. The median is not the only message: a clinician's perspective on mathematical analysis of glycemic variability and modeling in diabetes mellitus. J Diabetes Sci Technol. 2009;3(1):3-11.
9. Service FJ, Molnar GD, Rosevear JW, Ackerman E, Gatewood LC, Taylor WF. Mean amplitude of glycemic excursions, a measure of diabetic instability. Diabetes. 1970;19(9):644-55.
10. Kovatchev B, Clarke W, Breton M, Brayman K, McCall A. Quantifying temporal glucose variability in diabetes via continuous glucose monitoring: mathematical methods and clinical application. Diabetes Technol Ther. 2005;7(6):849-62.

11. Kovatchev B, Otto E, Cox D, Gonder-Frederick L, Clarke W. Evaluation of a new measure of blood glucose variability in diabetes. Diabetes Care. 2006;29(11):2433-8.
12. Hill NR, Hindmarsh PC, Stevens RJ, Stratton IM, Levy JC, Matthews DR. A method for assessing quality of control from glucose profiles. Diabet Med. 2007;24(7):753-8.
13. Kovatchev B. Assessment of risk for severe hypoglycemia among adults with IDDM: validation of the low blood glucose index. Diabetes Care. 1998;21(11):1870-5.
14. Kovatchev BP, Cox DJ, Gonder-Frederick L, Clarke WL. Methods for quantifying self-monitoring blood glucose profiles exemplified by an examination of blood glucose patterns in patients with type 1 and type 2 diabetes. Diabetes Technol Ther. 2002;4(3):295-303.
15. Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. Diabetes. 2005;54(6):1615-25.
16. Monnier L, Mas E, Ginet C, Michel F, Villon L, Cristol JP, Colette C. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. JAMA. 2006;295(14):1681-7.
17. Esposito K, Nappo F, Marfella R, Giugliano G, Giugliano F, Ciotola M, Quagliaro L, Ceriello A, Giugliano D. Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans: role of oxidative stress. Circulation. 2002;106(16):2067-72.
18. Quagliaro L, Piconi L, Assaloni R, Martinelli L, Motz E, Ceriello A. Intermittent high glucose enhances apoptosis related to oxidative stress in human umbilical vein endothelial cells the role of protein kinase C and NAD(P)H-oxidase activation. Diabetes. 2003;52:2795-804.
19. Ceriello A, Quagliaro L, Piconi L, Assaloni R, Da Ros R, Maier A, Esposito K, Giugliano D. Effect of postprandial hypertriglyceridemia and hyperglycemia on circulating adhesion molecules and oxidative stress generation and the possible role of simvastatin treatment. Diabetes. 2004;53(3):701-10.
20. Quagliaro L, Piconi L, Assaloni R, Da Ros R, Maier A, Zuodar G, Ceriello A. Intermittent high glucose enhances ICAM-1, VCAM-1 and E-selectin expression in human umbilical vein endothelial cells in culture: the distinct role of protein kinase C and mitochondrial superoxide production. Atherosclerosis. 2005;183(2):259-67.
21. Ihnat M, Thorpe J, Ceriello A. Hypothesis: the 'metabolic memory', the new challenge of diabetes. Diabet Med. 2007;24(6):582-6.
22. Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA1c. Diabetes Care. 2003;26(3):881-5.
23. Monnier L, Colette C, Dunseath G, Owens D. The loss of postprandial glycemic control precedes stepwise deterioration of fasting with worsening diabetes. Diabetes Care. 2007;30(2):263-9.
24. The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. Diabetes. 1995;44(8):968-83.
25. Mohsin F, Craig ME, Cusumano J, Chan AK, Hing S, Lee JW, Silink M, Howard NJ, Donaghue KC. Discordant trends in microvascular complications in adolescents with type 1 diabetes from 1990 to 2002. Diabetes Care. 2005;28(8):1974-80.
26. Gimeno-Orna J, Castro-Alonso F, Boned-Juliani B, Lou-Arnal L. Fasting plasma glucose variability as a risk factor of retinopathy in Type 2 diabetic patients. J Diabetes Complications. 2003;17(2):78-81.
27. Bragd J, Adamson U, Bäcklund L, Lins P, Moberg E, Oskarsson P. Can glycaemic variability, as calculated from blood glucose self-monitoring, predict the development of complications in type 1 diabetes over a decade? Diabetes Metab. 2008; 34(6):612-6.
28. Kilpatrick ES, Rigby AS, Atkin SL. A1C variability and the risk of microvascular complications in type 1 diabetes: data from the Diabetes Control and Complications Trial. Diabetes Care. 2008;31(11):2198-202.
29. Donahue R, Abbott R, Reed D, Yano K. Postchallenge glucose concentration and coronary heart disease in men of Japanese ancestry. Honolulu Heart Program. Diabetes. 1987;36(6):689-92.
30. Lowe L, Liu K, Greenland P, Metzger B, Dyer A, Stamler J. Diabetes, asymptomatic hyperglycemia, and 22-year mortality in black and white men. The Chicago Heart Association Detection Project in Industry Study. Diabetes Care. 1997;20(2):163-9.
31. Balkau B, Shipley M, Jarrett R, Pyörälä K, Pyörälä M, Forhan A, Eschwège E. High blood glucose concentration is a risk factor for mortality in middle-aged nondiabetic men. 20-year follow-up in the Whitehall Study, the Paris Prospective Study, and the Helsinki Policemen Study. Diabetes Care. 1998;21(3):360-7.
32. De Vegt F, Dekker JM, Ruhè HG, Stehouwer CD, Nijpels G, Bouter LM, Heine RJ. Hyperglycaemia is associated with all-cause and cardiovascular mortality in the Hoorn population: the Hoorn Study. Diabetologia. 1999;42(8):926-31.
33. Esposito K, Ciotola M, Carleo D, Schisano B, Sardelli L, Di Tommaso D, Misso L, Saccomanno F, Ceriello A, Giugliano D. Post-meal glucose peaks at home associate with carotid intima-media thickness in type 2 diabetes. J Clin Endocrinol Metab. 2008;93(4):1345-50.
34. Hanefeld M, Fischer S, Julius U, Schulze J, Schwanebeck U, Schmechel H, Ziegelasch HJ, Lindner J. Risk factors for myocardial infarction and death in newly detected NIDDM: the Diabetes Intervention Study, 11-year follow-up. Diabetologia. 1996;39(12):1577-83.
35. Cavalot F, Petrelli A, Traversa M, Bonomo K, Fiora E, Conti M, Anfossi G, Costa G, Trovati M. Postprandial blood glucose is a stronger predictor of cardiovascular events than fasting blood glucose in type 2 diabetes mellitus, particularly in women: lessons from the San Luigi Gonzaga Diabetes Study. J Clin Endocrinol Metab. 2006;91(3):813-9.
36. Esposito K, Giugliano D, Nappo F, Marfella R. Regression of carotid atherosclerosis by control of postprandial hyperglycemia in type 2 diabetes mellitus. Circulation. 2004;110(2):214-9.
37. Chiasson J, Josse R, Gomis R, Hanefeld M, Karasik A, Laakso M. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance. The STOP-NIDDM Trial. JAMA. 2003;290(4):486-94.
38. Wentholt I, Kulik W, Michels R, Hoekstra J, DeVries J. Glucose fluctuations and activation of oxidative stress in patients with type 1 diabetes. Diabetologia. 2008;51(1):183-90.
39. Derr R, Garrett E, Stacy GA, Saudek CD. Is HbA(1c) affected by glycemic instability? Diabetes Care. 2003;26(10):2728-33.
40. McCarter RJ, Hempe JM, Chalew SA. Mean blood glucose and biological variation have greater influence on HbA1c levels than glucose instability: an analysis of data from the Diabetes Control and Complications Trial. Diabetes Care. 2006;29(2):352-5.
41. Kohnert KD, Augstein P, Heinke P, Zander E, Peterson K, Freyse EJ, Salzsieder E. Chronic hyperglycemia but not glucose variability determines HbA1c levels in well-controlled patients with type 2 diabetes. Diabetes Res Clin Pract. 2007;77(3):420-6.
42. Kilpatrick ES, Rigby AS, Atkin SL. The effect of glucose variability on the risk of microvascular complications in type 1 diabetes. Diabetes Care. 2006;29(7):1486-1490.
43. Kilpatrick ES, Rigby AS, Atkin SL. Variability in the relationship between mean plasma glucose and HbA1c: implications for the assessment of glycemic control. Clin Chem. 2007;53(5):897-901.

44. Pankow J, Kwan D, Duncan B, Schmidt M, Couper D, Golden S, Ballantyne CM. Cardiometabolic risk in impaired fasting glucose and impaired glucose tolerance: the Atherosclerosis Risk in Communities Study. Diabetes Care. 2007;30(2):325-31.

45. Barr E, Zimmet P, Welborn T, Jolley D, Magliano D, Dunstan D, Cameron AJ, Dwyer T, Taylor HR, Tonkin AM, Wong TY, McNeil J, Shaw JE. Risk of cardiovascular and all-cause mortality in individuals with diabetes mellitus, impaired fasting glucose, and impaired glucose tolerance: the Australian Diabetes, Obesity, and Lifestyle Study (AusDiab). Circulation. 2007;116(2):151-7.

46. The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008;358(24):2545-59.

47. The ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompoint S, de Galan BE, Joshi R, Travert F.Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008;358(24):2560-72.

48. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, Zieve FJ, Marks J, Davis SN, Hayward R, Warren SR, Goldman S, McCarren M, Vitek ME, Henderson WG, Huang GD; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med. 2009;360(2):129-39.

49. Kilpatrick ES, Rigby AS, Atkin SL. Mean blood glucose compared with HbA1c in the prediction of cardiovascular disease in patients with type 1 diabetes. Diabetologia. 2008;51(2):365-71.

50. Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis. JAMA. 2007;298(2):194-206.