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Glycemic Variability: Clinical and Prognostic Significance

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ABSTRACT

Minimizing development or progression of chronic diabetic micro and macro-vascular complications has been always the goal of glycemic control. In recent years, much attention has been focused on the possibility that glycemic variability confers an additional risk factor for diabetic complications independent of glycated hemoglobin (HbA1c). Evidence suggests that fluctuating glucose levels produce endothelial dysfunction as well as an increase in free radicals, the key link between hyperglycemia and diabetic complications and that these changes are greater than those produced by sustained hyperglycemia in *in vitro* and in animal studies. In humans studies, experimental setting also support the hypothesis that plasma glucose fluctuations produce a higher increase in oxidative stress as well as endothelial dysfunction than those produced by sustained hyperglycemia in type 2 diabetes. Moreover, glycemic variability may have a role in the prediction of severe hypoglycemia, which may act as a precipitating factor of diabetic complications. Based on review of available evidence, we advocate decreasing hyperglycemia and diminishing glycemic variability as well as avoiding hypoglycemia in diabetic patients as targets of diabetic therapy. Future trials targeting the influence of the control of plasma glucose fluctuations on the development of diabetic micro-and macro-vascular complications are needed to further strengthen the evidence base.

KEYWORDS: Type 1 diabetes; Type 2 diabetes; Glycemic variability; Diabetic complications.

ABBREVIATIONS: HbA1c: glycated hemoglobin; FPG-CV: Coefficient of variation of fasting plasma glucose; SD: Standard Deviation; SMBG: Self-monitoring blood glucose; MAGE: Mean Amplitude of Glycemic Excursions; SDBG: Standard Deviation of Blood Glucose; MBG: Mean Blood Glucose; M-FPG: Magnitude of hyperglycemia.

INTRODUCTION

Diabetes is ranked among the leading causes of morbidity and mortality, and is a tremendous cost burden in medical care.[1,2] Although glycated hemoglobin (HbA1c) has been considered the surrogate endpoint for long-term glycemic control; recent evidence has raised the question that plasma glycemic variability, irrespective of HbA1c level, may confer an addition risk for the development of diabetic complications.[3,4]

Several large prospective clinical studies suggest the possibility of glycemic variation may be the explanation for microvascular complication difference between intensively treated and conventionally treated type 1 diabetes patients.[5-7] Furthermore, there were no significant associations between tighter HbA1c control and cardiovascular risk reduction in the landmark studies in patients with type 2 diabetes: Action to Control Cardiovascular Risk in Diabetes (AC-

CORD), Action in Diabetes and Vascular Disease (ADVANCE), and Veteran Administration Diabetes Trial (VADT).[8–10] It has been suggested that the one of these determining factors is the frequency and magnitude of glycemic variation.[11] Moreover, there is increasing evidence in recent studies suggesting a positive link between glycemic variability, as measured by Coefficient of variation (CV) of Fasting Plasma Glucose (FPG), and the risk of developing ischemic stroke as well as all-cause, cancer and cardiovascular mortality in type 2 diabetic patients.[12-19]

In this review article, we firstly provide an overview of the various methods to measure glycemic variability. Secondly, we intend to assess the published evidence investigating glycemic variability and the development of microvascular complications (e.g. retinopathy, neuropathy, and nephropathy) and macrovascular complications (e.g. cerebrovascular disease, coronary artery disease, and peripheral artery disease) in type 1 and type 2 diabetes patients. Thirdly, we review laboratory studies investigating the issue of glycemic variability. Lastly, key issues regarding glycemic variability will be summarized in the conclusion.

MEASUREMENTS FOR GLYCEMIC VARIABILITY

To quantify glycemic variability, several methods have been suggested but no "gold standard" has been universally accepted. More detailed descriptions of various methods have been described elsewhere in one review article, and we just briefly introduce commonly used measurements herein.[20] Overall, glycemic variability may be determined as interday or intraday variation. Glycemic intraday variation reflects the swings of plasma glucose in a diabetic patient as a consequence of diminished or absent auto regulations of sugar control within-day. The simplest and most common way to measure glycemic variability is to calculate the Standard Deviation (SD) of mean blood glucose and Coefficient of variation (CV), if one wishes to correct for the mean.[20] It is possible to calculate SD and CV from seven-point glucose curves by Self-monitoring blood glucose (SMBG).[20-23] However, obstacles arose from using seven-point glucose curves because certain peak or bottom values will always be missing between the two measurements, making it less accurate.[20] Another widely deployed method, Mean Amplitude of Glycemic Excursions (MAGE), was first proposed from Service, et al. measuring the differences between peaks and bottoms around a mean glucose value greater than one SD of mean blood glucose for 48 hours.[21] It was designed to disregard small fluctuations and focus on major glucose fluctuations.

The easiest way to measure interday variability is to calculate the SD of mean blood glucose and CV. However, it requires data from at least 2 consecutive days to calculate and it neglects within-day blood glucose variations. The other method used to measure interday glucose variability, Mean of daily differences (MODD), was proposed by Molnar, et al. to calculate the mean of absolute differences between glucose levels at corresponding time on two consecutive days.[22] However, it appears to be a challenge in daily practice as mealtime variation will affect interfering the measurement.

Each of these tools has its own advantages and disadvantages; while some are easy to apply, others are more complex and are not practical for clinical use.[23] Future research must compare different methods in assessing glycemic variability and investigate predictive capacity of glucose variance for medical outcome in diabetes patients.

LABORATORY EVIDENCE FOR GLYCEMIC VARIABILITY

Evidence has suggested endothelial dysfunction and formation of reactive oxygen species as the key link between hyperglycemia and diabetic complications.[24] *In vitro* studies have shown that exposure of cell cultures to rapid glucose fluctuations produced more severe cellular damage as compared with continuous high glucose.[25,26] Evidence also suggests that oscillating plasma glucose proves more deleterious than constant high glucose on oxidative-stress generation, important factors in micro-and macroangiopathy.[27-30] Experiments in animals also support the hypothesis that fluctuating glucose significantly induced monocyte-endothelial adhesion and atherogenesis as compared with sustained hyperglycemia.[31-33]

Production of free radicals, accompanied by inadequate intracellular anti-oxidant defenses seems to account for this phenomenon.[34] Similarly, in humans, two studies assessed the effect of fluctuations of plasma glucose producing on oxidative stress among patients with type 2 diabetes. These authors found that oscillating glucose was more damaging to endothelial function and resulted in higher levels of oxidative stress markers as compared with sustained hyperglycemia in type 2 diabetes.[35,36] On the other hand, it is somewhat amazing and difficult to explain that such a relationship between glycemic variability and elevated levels of oxidative stress could not be confirmed in patients with type 1 diabetes.

More specifically, glucose fluctuations appear more relevant to atherosclerosis progression in type 2 diabetics than those with sustained hyperglycemia.[37,38] This is also supported by the evidence that change in intima-media thickness, a marker of endothelial dysfunction, was associated with a reduction in daily glucose excursions, but not indices of chronic sustained hyperglycemia.[39,40]

GLYCEMIC VARIABILITY AND MICROVASCULAR COMPLICATIONS IN TYPE 1 DIABETES

Bragd, et al. initiated a cohort study to examine the linkage between glycemic variability measured by Standard Deviation of Blood Glucose (SDBG) for 4 weeks and the development of microvascular complications in type 1 diabetes. After 11-years followed up, authors concluded that glycemic variabil-

ity was a predictor of prevalence but not incidence of peripheral neuropathy. No significant relationship toward to the development of retinopathy and nephropathy was found.[41] Kilpatrick, et al. began series of studies using DCCT data to access the correlation between glycemic variability measured by Mean Blood Glucose (MBG) and risk of developing diabetic retinopathy and nephropathy complications during the 9-years follow up as well as risk in developing cardiovascular diseases, which will be discussed later in this article.[42,43] Results revealed that MBG was associated significantly with the development of retinopathy but not nephropathy. Similarly, Service, et al. utilizing DCCT data to assess the development of diabetic retinopathy by 7-point capillary glucose profiles collected at quarterly intervals for a period of minimal 4-years.[21] Cox regression analysis revealed MBG was significantly associated with retinopathy. Moberg, et al. investigated the association between twenty-four different clinical parameters and glycemic variability in type 1 diabetes patients with intense insulin therapy, significant association between glycemic variability and the presence of nephropathy was found.[44] However, retinopathy and neuropathy were not associated with glycemic variability in this study.

GLYCEMIC VARIABILITY AND MACROVASCULAR COMPLICATIONS IN TYPE 1 DIABETES

As for macrovascular complications in male patients with type 1 diabetes, Gordin, et al. assessed the association of glycemic variability toward arterial stiffness, an early sign of macrovascular complications.[45] Interestingly, arterial stiffness was correlated with MBG but not with MAGE at baseline. Furthermore, none of measurements were associated with arterial stiffness during the hyperglycaemic clamp. As mentioned previously, Kilpatrick, et al. using DCCT trial data to investigate whether there are relationship between glucose control (MBG, HbA1c and intraday SDBG) and the risk of developing cardiovascular diseases. Results showed significantly relationship between MBG, pre-prandial, and postprandial blood glucose to the risk of developing cardiovascular diseases but not with HbA1c and glucose variability.[42,43] Hence, there is no evidence between glycemic variability as well as HbA1c to macrovascular risk among DCCT trial.

GLUCOSE VARIABILITY AND MICROVASCULAR COMPLICATIONS IN TYPE 2 DIABETES

Gimeno-Orma, et al. investigated in a 5-year follow up prospective cohort study whether glycemic variability (measured by the FPG-CV quartiles) can be an independent predictor for diabetic retinopathy.[46] The results showed that patients suffered from diabetic retinopathy had higher FPG-CV values and there was an increased trend of diabetic retinopathy with increased FPG quartiles. In the Verona Diabetes Study conducted in Italy, during the cross-sectional analysis, FPG-CV was significant associated with the presence of diabetic retinopathy. However, after a mean interval of 1.6 years between the first and second eye evaluation, this study found the magnitude of hyperglycemia (M-FPG) and HbA1c not the FPG-CV as a strong independent predictor for the development and progression of diabetic retinopathy in type 2 diabetes patients.[47]

GLYCEMIC VARIABILITY AND MACROVASCULAR COMPLICATIONS IN TYPE 2 DIABETES

In recent year, the Verona Diabetes Study focused on whether long-term glucose control as assessed by fasting plasma glucose is a predictor of all-causes mortality and cardiovascular diseases related mortality among a cohort of patients with type 2 diabetes who are aged≥75 years.[12,13] Results revealed that glucose variability has a greater effect on survival in elderly patients with type 2 diabetes and authors concluded that the glucose instability measured by FPG-CV was the predictor of cardiovascular diseases related mortality. Furthermore, two extensions of the same study assessing among patients with different age group (aged between 56-74 years, aged<65 year, and aged≥65 years) further proved that variability of FPG independently increased the risk of all-cause mortality in patients with type 2 diabetes.[14,15] Similarly, the Taichung Diabetes Study conducted in Taiwan, have demonstrated that FPG-CV is an independent predictor of all-cause or cause specific mortality in type 2 diabetic patients.[17,18] Furthermore, the same group initiated the Taiwan Diabetes Study, a large population-based retrospective study, 28,354 type 2 diabetic, aged≥30 years and free of ischemic stroke patients were selected from National Diabetes Care Management Program (NDCMP). The patients were grouped into four quartiles according to FPG-CV measurements.[19] The results revealed that compared to patients with the first quartile, higher associated risk of developing ischemic stroke in patients who fell into second, third, and fourth FPG-CV quartile, independent of HbA1c level.

GLYCEMIC VARIABILITY AND HYPOGLYCEMIA COMPLICATIONS

Severe hypoglycemia can lead to severe consequences, such as coma and death. Many harmful events could be avoided if it were possible to predict severe hypoglycemia. Both Cox, et al. and The Diabetes Outcome in Veterans Study (DOVES) suggested that glycemic variability may be a potential predictor of future hypoglycemia occurrence.[48,49] Furthermore, glycemic variability if accompanied with severe hypoglycemia episodes may adversely alter the prognosis of acutely ill patients[50,51] It has also been shown that hyperglycemia after hypoglycemia could be more hazardous than that when hypoglycemia is followed by normoglycemia.[52] One can argue that much of risk in long-term microvascular and macrovascular complications could be avoided by focusing merely in reduction of hypoglycemic episodes. However, in the Taiwan Diabetes Study, FPG-CV still showed links with incidence of ischemic stroke after excluding patients with hypoglycemia in sensitivity analysis; this association cannot

be explained by hypoglycemia in patients with high glucose variability.[19] Further studies need to investigate the effects of glycemic variability whether co-existence of hypoglycemia or not for diabetic complications.

CONCLUSION

For the past two decades, glycemic variability is of great interest to the diabetes community. Studies have focused on correlation between glycemic variability and diabetic complications, methods to measure glycemic variability, and understanding mechanisms driving glycemic variation. There is increasing evidence in *in vitro*, animal studies and in an experimental setting in type 2 diabetes patients suggesting that glycemic variability is closely associated with the pathogenesis of diabetic complications. In clinical settings, accumulating evidence suggests that, in addition to and independently of HbA1c, glycemic variability may play an important part in the development of diabetic complications. However, No 'gold standard' currently exists to rate glycemic variability. Setting universally accepted measurements, methodologies is mandatory. Lowering HbA1c and diminishing glycemic variability as well as avoiding hypoglycemia should be crucial steps in reducing complications or mortality in diabetes patients. We advocate following the 2015 revision of American Diabetic Association (ADA) guidelines for a tighter glycemic control in early disease course as well as avoidance of extreme blood glucose fluctuations to effectively prevent or delay the development of diabetic complications both in type 1 and type 2 diabetes.[1,53]

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REFERENCES

1. American Diabetes Association. Standard of medical care in diabetes - 2015. *Diabetes Care*. 2015; 38: S4-S69.

2. The American Heart Association and American Stoke Association. Guidelines for the primary prevention of stoke: A guideline for healthcare professional. *Stoke*. 2011; 42: 517-584.

3. Brownlee M, Hirsch IB. Glycemic variability: a hemoglobin A1c independent risk factor for diabetic complications. *JAMA*. 2006; 295: 1707-1782.

4. Hirsch IB, Brownlee M. Should minimal blood glucose variability become the gold standard of glycemic control? *J Diabetes Complications*. 2005; 19: 178-181.

5. The effect of intensive treatment of diabetes on the development and progression of long-term complication in insulin-dependent diabetes mellitus. The Diabetes Control and Complication Trial Research Group. *N Engl J Med*. 1993; 329: 977-986. doi: 10.1056/NEJM199309303291401

6. The relationship of glycemic exposure (hba1c) to the risk of development and progression of retinopathy in the diabetes control and complication trail. The Diabetes Control and Complications Trial Research Group. *Diabetes*. 1995; 44: 968-983.

7. The diabetes control and complication trail/epidemiology of diabetes interventions and complication research group. Effect of intensive therapy on the microvascular complication of type 1 diabetes mellitus. *JAMA*. 2002; 287: 2563-2569.

8. Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008; 358: 2545-2559. doi: 10.1056/NEJMoa0802743

9. Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2008; 358: 2560-2572. doi: 10.1056/NEJMoa0802987

10. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med*. 2009; 360: 129-139. doi: 10.1056/NEJMoa0808431

11. Cavalot F. Do data in the literature indicate that glycaemic variability is a clinical problem? Glycaemic variability and vascular complications of diabetes. *Diabetes Obes Metab*. 2013: 15: 3-8. doi: 10.1111/dom.12140

12. Muggeo M, Verlato G, Bonora E, et al. Long-term instability of fasting plasma glucose predicts mortality in elderly NIDDM patients: the Verona Diabetes Study. *Diabetologia*. 1995; 38: 672-679.

13. Muggeo M, Verlato G, Bonora E, Zoppini G, Corbellini M, de Marco R. Long-term instability of fasting plasma glucose, a novel predictor of cardiovascular mortality in elderly patients with non-insulin-dependent- diabetes mellitus: the Verona Diabetes Study. *Circulation*. 1997; 96: 1750-1754.

14. MuggeoM, Zoppini G, Bonora E, et al. Fasting plasma glucose variability predicts 10-year survival of type 2 diabetes patients: the Verona Diabetes Study. *Diabetes Care*. 2000; 23: 45-50.

15. Zoppini G, Verlato G, Targher G, et al. Variability of body weight, plus pressure and glycaemia strongly predict total mortality in elderly type 2 diabetic patients. The Verona Diabetes Study. *Diabetes Metab Res Rev*. 2008; 24: 624-628. doi: 10.1002/dmrr.897

16. MuggeoM, Verlato G, Bonora E, et al. The Verona Diabetes Study: a population-based survey on known diabetes mellitus prevalence and 5-year all-cause mortality. *Diabetologia*. 1995; 38: 318-325.

17. Lin CC, Li CI, Yang SY, et al. Variation of fasting plas-

ma glucose: a predictor of mortality in patients with type 2 diabetes. *Am J Med*. 2012; 125: 416. e9-e18. doi: 10.1016/j.amjmed.2011.07.027

18. Lin CC, Li CI, Liu CS, et al. Annual fasting plasma glucose variation increases risk of cancer incidence and mortality in patients with type 2 diabetes: The Taichung Diabetes Study. *Endocr Relat Cancer*. 2012; 19: 473-483. doi: 10.1530/ERC-12-0038

19. Lin CC, Yang CP, Li CI, et al. Visit-to-visit variability of fasting plasma glucose as predictor of ischemic stroke: competing risk analysis in a national cohort of Taiwan Diabetes Study. *BMC Med*. 2014; 12: 165. doi: 10.1186/s12916-014-0165-7

20. Siegelaar S, Holleman F, Hoekstra J, DeVries JH. Glucose variability; Does it matter? *Endocrine Rev*. 2010; 31: 171-182. doi: 10.1210/er.2009-0021

21. Service FJ, O'Brien PC. The relation of glycaemia to the risk of development and progression of retinopathy in the Diabetic Control and Complications Trial. *Diabetologia*. 2001; 44: 1215-1220.

22. Molnar GD, Taylor WF, Ho MM. Day-to-day variation of continuously monitored glycaemia: a further measure of diabetic instability. *Diabetologia*. 1972; 8: 342-348.

23. Eslami S1, Taherzadeh Z, Schultz MJ, Abu-Hanna A. Glucose variability measures and their effect on mortality: a systematic review. *Intensive Care Med*. 2011; 37: 583-593. doi: 10.1007/s00134-010-2129-5

24. Ceriello A, Ihnat MA. Glycemic variability: a new therapeutic challenge in diabetes and the critical care setting. *Diabet Med*. 2010; 27: 862-867. doi: 10.1111/j.1464-5491.2010.02967.x

25. Risso A, Mercuri F, Quagliaro L, DamanteG, Ceriello A. Intermittent high glucose enhances apoptosis in human umbilical vein endothelial cells in culture. *Am J Physiol Endocrinol Metab*. 2001; 281: E924-E930.

26. Del Guerra S, Grupillo M, Masini M, et al. Gliclazide protects human islet beta-cells from apoptosis induced by intermittent high glucose. *Diabetes Metab Res Rev*. 2007; 23: 234-238.

27. Quagliaro L, Piconi L, Assaloni R, Martinelli L, MotzE, 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: 2795-2804.

28. Piconi L, Quagliaro L, Da Ros R, et al. Intermittent high glucose enhances ICAM-1, VCAM-1, Eselectin and interleukin-6 expression in human umbilical endothelial cells in culture: the role of poly(ADP-ribose) polymerase. *J Thromb Haemost*. 2004; 2: 1453-1459.

29. Quagliaro L, Piconi L, Assaloni R, et al. Intermittent high glucose enhances ICAM-1, VCAM-1 and Eselectin expression in human umbilical vein endothelial cells in culture: the distinct role of protein kinase C and mitochondrial superoxide production. *Atherosclerosis*. 2005; 183: 259-267.

30. Piconi L, Quagliaro L, Assaloni R, et al. Constant and intermittent high glucose enhances endothelial cell apoptosis through mitochondrial superoxide overproduction. *Diabetes Metab Res Rev*. 2006; 22: 198-203.

31. Azuma K, Kawamori R, Toyofuku Y, et al. Repetitive fluctuations in blood glucose enhance monocyte adhesion to the endothelium of rat thoracic aorta. *Arterioscler ThrombVasc Biol*. 2006; 26: 2275-2280.

32. Mita T, Otsuka A, Azuma K, et al. Swings in blood glucose levels accelerate atherogenesis in apolipoprotein E-deficient mice. *Biochem Biophys Res Commun*. 2007; 358: 679-685.

33. Azuma K, Toyofuku Y, Iesaki T, et al. Acarbose, an a-glucosidase inhibitor, improves endothelial dysfunction in Goto-Kakizaki rats exhibiting repetitive blood glucose fluctuation. *Biochem Biophys Res Commun*. 2006; 345: 688-693.

34. Nalysnyk L, Hernandez-Medina M, Krishnarajah G. Glycaemic variability and complications in patients with diabetes mellitus: evidence from a systematic review of the literature. *Diabetes Obes Metab*. 2010; 12: 288-298. doi: 10.1111/j.1463-1326.2009.01160.x.

35. Monnier L, Mas E, Ginet C, et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *JAMA*. 2006; 295: 1681-1687.

36. Ceriello A, Esposito K, Piconi L, et al. Oscillating glucose is more deleterious to endothelial function and oxidative stress than mean glucose in normal and type 2 diabetic patients. *Diabetes*. 2008; 57: 1349-1354. doi: 10.2337/db08-0063

37. Hu Y, Liu W, Huang R, Zhang X. Post challenge plasma glucose excursions, carotid intima-media thickness, and risk factors for atherosclerosis in Chinese population with type 2 diabetes. *Atherosclerosis*. 2010; 210: 302-306. doi: 10.1016/j.atherosclerosis.2009.11.015

38. Temelkova-Kurktschiev TS, Koehler C, Henkel E, Leonhardt W, Fuecker K, HanefeldM. Post challenge plasma glucose and glycemic spikes are more strongly associated with atherosclerosis than fasting glucose or HbA1c level. *Diabetes Care*. 2000; 23: 1830-1834.

39. Barbieri M, Rizzo MR, Marfella R, et al. Decreased ca-

rotid atherosclerotic process by control of daily acute glucose fluctuations in diabetic patients treated by DPP-IV inhibitors. *Atherosclerosis*. 2013; 227: 349-354. doi: 10.1016/j.atherosclerosis.2012.12.018

40. Wentholt IM, Kulik W, Michels RP, Hoekstra JB, DeVries JH. Glucose fluctuations and activation of oxidative stress in patients with type 1 diabetes. *Diabetologia*. 2008; 51: 183-190.

41. Bragd J, Adamson U, Bäcklund LB, Lins PE, Moberg E, Oskarsson P. Can glycemic variability, as calculated from blood glucose self-monitoring, predict the development of complication in type 1 diabetes, over a decade? *Diabetes Metab*. 2008; 34: 612-616. doi: 10.1016/j.diabet.2008.04.005

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: 1486-1490.

43. 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: 365-371.

44. Moberg EA, Lins PE, Adamson UK. Variability of blood glucose levels in patients with type 1 diabetes mellitus on intensified insulin regimens. *Diabetes Metab*. 1994; 20: 546-552.

45. Gordin D, Ronnback M, Forsblom C, Mäkinen V, Saraheimo M, Groop PH. Glucose variability, blood pressure and arterial stiffness in type 1 diabetes. *Diabetes Res Clin Pract*. 2008; 80: e4-e7. doi: 10.1016/j.diabres.2008.01.010

46. Gimeno-Orna JA, Castro-Alonso FJ, Boned-Juliani B, Lou-Arnal LM. Fasting plasma glucose variability as a risk factor of retinopathy in type 2 diabetic patients. *J Diabetes Complications*. 2003; 17: 78-81.

47. Zoppini G, Verlato G, Targher G, et al. Is fasting glucose variability a risk factor for retinopathy in people with type 2 diabetes? *Nutr Metab Cardiovasc Dis*. 2009; 19: 334-339. doi: 10.1016/j.numecd.2008.02.007

48. Cox DJ, Kovatchev BP, Julian DM, et al. Frequency of severe hypoglycemia in insulin-dependent diabetes mellitus can be predicted from self-monitoring blood glucose data. *J Clin Endocrinol Metab*. 1994; 79: 1659-1662.

49. Murata GH, Hoffman RM, Shah JH, Wendel CS, Duckworth WC. A probabilistic model for predicting hypoglycemia in type 2 diabetes mellitus: the Diabetes Outcomes in Veterans Study (DOVES). *Arch Intern Med*. 2004; 164: 1445-1450.

50. Zoungas S, Patel A, Chalmers J, et al. ADVANCE Collaborative Group: Severe hypoglycemia and risks of vascular events and death. *N Engl J Med*. 2010; 363: 1410-1418. doi: 10.1056/NEJMoa1003795

51. Yakubovich N, Gerstein HC. Serious cardiovascular outcomes in diabetes: the role of hypoglycemia. *Circulation*. 2011; 123: 342-348. doi: 10.1161/CIRCULATIONAHA.110.948489

52. Ceriello A, Novials A, Ortega E, et al. Evidence that hyperglycemia after recovery from hypoglycemia worsens endothelial function and increases oxidative stress and inflammation in healthy control subjects and subjects with type 1 diabetes. *Diabetes*. 2012; 61: 2993-2997. doi: 10.2337/db12-0224

53. Standards of medical care in diabetes 2015: summary of revisions. *Diabetes Care*. 2015; 8: S4. doi: 10.2337/dc15-S003