



Glucose Concentrations of Less Than 3.0 mmol/L (54 mg/dL) Should Be Reported in Clinical Trials: A Joint Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes

Diabetes Care 2017;40:155-157 | DOI: 10.2337/dc16-2215

The International Hypoglycaemia Study Group recommends that the frequency of detection of a glucose concentration < 3.0 mmol/L (<54 mg/dL), which it considers to be clinically significant biochemical hypoglycemia, be included in reports of clinical trials of glucose-lowering drugs evaluated for the treatment of diabetes mellitus.

The glycemic thresholds for symptoms of hypoglycemia and for glucose counter-regulatory (including sympathoadrenal) responses to hypoglycemia, as plasma glucose concentrations fall, are not fixed in patients with insulin-, sulfonylurea-, or meglitinide (glinide)-treated diabetes. They are at higher glucose concentrations in those with poor glycemic control and at lower glucose concentrations in those with tight glycemic control (1–5). The shifts in glycemic threshold to lower glucose concentrations are largely the result of more frequent episodes of iatrogenic hypoglycemia during intensive glycemic therapy. Glycemic thresholds for responses to hypoglycemia vary, not only among individuals with diabetes but also in the same individual with diabetes as a function of their HbA $_{1c}$ levels and hypoglycemic experience; it is therefore not appropriate to cite a specific glucose concentration that defines hypoglycemia in diabetes. As a consequence, the American Diabetes Association has defined hypoglycemia in diabetes nonnumerically as "all episodes of an abnormally low plasma glucose concentration that expose the individual to potential harm" (6,7).

Nonetheless, the International Hypoglycaemia Study Group believes that it is important to identify and record a level of hypoglycemia that needs to be avoided because of its immediate and long-term danger to the individual. A single glucose level should be agreed to that has serious clinical and health-economic consequences. This would enable the diabetes and regulatory communities to compare the effectiveness of interventions in reducing hypoglycemia, be they pharmacological, technological, or educational. It would also permit the use of meta-analysis as a statistical tool to increase power when comparing interventions.

In its discussion, the International Hypoglycaemia Study Group considered glucose concentration levels of <3.0 mmol/L (<54 mg/dL) and <2.8 mmol/L (<50 mg/dL) detected by self-monitoring of plasma glucose, continuous glucose monitoring (for at least 20 minutes), or a laboratory measurement of plasma glucose. Both of these levels are distinctly low glucose concentrations that do not occur under physiological conditions in nondiabetic individuals (8). Thus, they are unequivocally hypoglycemic values. They approximate the upper and lower limits, respectively, of the nondiabetic glycemic threshold for symptoms of insulin-induced hypoglycemia (8–10). The generic nondiabetic glycemic threshold for impairment of cognitive

International Hypoglycaemia Study Group*

Corresponding author: Simon R. Heller, s.heller@sheffield.ac.uk.

This position statement was reviewed and approved by the American Diabetes Association Professional Practice Committee in September 2016 and ratified by the American Diabetes Association Board of Directors in October 2016.

*Members of the International Hypoglycaemia Study Group are listed in the APPENDIX.

This article is being simultaneously published in Diabetes Care and Diabetologia by the American Diabetes Association and the European Association for the Study of Diabetes.

© 2017 by the American Diabetes Association and Springer-Verlag. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. More information is available at http://www.diabetesjournals.org/content/license.

Table 1—Proposed glucose levels when reporting hypoglycemia in clinical trials Level 1

A glucose alert value of 3.9 mmol/L (70 mg/dL) or less. This need not be reported routinely in clinical studies, although this would depend on the purpose of the study

A glucose level of \leq 3.0 mmol/L (\leq 54 mg/dL) is sufficiently low to indicate serious, clinically important hypoglycemia

Level 3

Severe hypoglycemia, as defined by the ADA (6,7), denotes severe cognitive impairment requiring external assistance for recovery

function is <2.8 mmol/L (<50 mg/dL) (8-10), but higher glucose levels have been reported for some tests (11-14). Glucose concentrations of both <3.0 mmol/L (<54 mg/dL) and <2.8 mmol/L (<50 mg/dL) cause defective glucose counterregulation and impaired awareness of hypoglycemia, the core components of hypoglycemia-associated autonomic failure in diabetes (5). Avoiding these glucose levels could reverse impaired awareness of hypoglycemia (15-18), and some aspects of defective glucose counterregulation (15-17), in many affected patients. In type 1 diabetes, failure to recognize one's own hypoglycemia at a glucose concentration <3.0 mmol/L (54 mg/dL) increased the risk of severe hypoglycemia (defined as needing the help of another person for recovery) fourfold (17). In type 2 diabetes, both glucose concentrations were associated with cardiac arrhythmias (19,20). Finally, a glucose concentration <2.8 mmol/L (<50 mg/dL) was associated with mortality in patients with type 2 diabetes in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (NCT00000620) (21), and possibly in the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial (NCT00069784) (22), and among patients treated in intensive care units in the Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial (NCT00220987) (23). A glucose concentration <3.0 mmol/L (<54 mg/dL) was associated with mortality in the NICE-SUGAR trial (23) and, possibly, in the ORIGIN trial (22).

Ultimately, the International Hypoglycaemia Study Group members agreed that a glucose concentration < 3.0 mmol/L (<54 mg/dL) is sufficiently low to indicate serious, clinically important hypoglycemia. Possible terms used to describe this

condition include "serious," "clinically important," "major," or "clinically significant." The group decided not to describe "severe hypoglycemia" in terms of glucose concentration since there is currently widespread agreement that severe hypoglycemia, as defined by the American Diabetes Association (6,7), denotes severe cognitive impairment requiring external assistance for recovery. The group also proposed that the frequency of detection of the glucose alert value of 3.9 mmol/L (70 mg/dL) or less (24) need not be reported routinely in clinical trials.

In conclusion we propose that the following glucose levels be adopted by the diabetes community to address the issue of hypoglycemic risk (Table 1).

Funding. The International Hypoglycaemia Study Group (IHSG) is supported through an unrestricted educational grant from Novo Nordisk awarded to Six Degrees Academy (SDA) of Toronto, Ontario, Canada. Along with the IHSG chair, SDA has been solely responsible for membership recruitment/selection and content/ outcomes for the meetings. The rationale for the formation of IHSG is that hypoglycemia is an under-recognized problem that deserves increased awareness and focus across the health care community. The group's ultimate goal is to improve the lives of patients with diabetes.

Duality of Interest. P.A. has served on scientific advisory boards and/or as a lecturer for AstraZeneca, Boehringer Ingelheim/Lilly, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, Merck Sharp & Dohme, Novartis, and Sanofi, B.C. has had research grant support from Halozyme and Lilly to the former MidAmerica Diabetes Associates. P.E.C. has served on scientific advisory boards for Novo Nordisk, B.E.d.G. has served on scientific advisory boards for Novo Nordisk and Sanofi and received research grant support from AstraZeneca, S.R.H. has served on scientific advisory boards and provided consultancy for which his institution has received remuneration from Lilly, Novo Nordisk, Takeda, Merck Sharp & Dohme, and Becton Dickinson; has served as a speaker for which he received remuneration from AstraZeneca, Lilly, Novo Nordisk, Boehringer Ingelheim, and Takeda; and has received research support from Medtronic

U.K. Ltd. B.M.F. has served on scientific advisory boards and as a speaker for Boehringer Ingelheim, Janssen, Merck Sharp & Dohme, Novo Nordisk, and Lilly. L.G.-F. has served as a consultant or speaker and/or has received research grant support from Abbott Diabetes Care, AstraZeneca, Dexcom, Johnson & Johnson, and Merck Sharp & Dohme. T.J. has served as a speaker for Novo Nordisk, Lilly, Medtronic, and Sanofi, K.K. has served as a consultant or speaker for AstraZeneca, Boehringer Ingelheim, Janssen, Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, and Sanofi and has received research grant support from AstraZeneca, Boehringer Ingelheim, Lilly, Novartis. Novo Nordisk. Roche, and Sanofi, L.A.L. has served as a consultant or speaker for Abbott, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Lilly, GlaxoSmithKline, Janssen, Merck Sharp & Dohme, Novo Nordisk, Sanofi, Servier, and Takeda, R.I.M. has served on scientific advisory boards for Novo Nordisk and Sanofi. E.R.S. has undertaken consultancy for Sanofi, Novo Nordisk, Lilly, Locemia, and Medtronic and received grant support from Lilly. R.V. is an employee and owns stock in Medtronic Inc. S.Z. has served on scientific advisory boards for Amgen, Bristol-Myers Squibb, AstraZeneca, Janssen, Merck Sharp & Dohme, Novo Nordisk, Sanofi, and Takeda; has served as a speaker for Bristol-Myers Squibb, AstraZeneca, Janssen, Merck Sharp & Dohme, Servier, and Takeda; and has received research grant support from Bristol-Myers Squibb and AstraZeneca. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. The issues discussed here were developed at meetings of the International Hypoglycaemia Study Group with a final meeting taking place on 9 June 2016.

Appendix

Members of the International Hypoglycaemia Study Group: Stephanie A. Amiel, RD, Lawrence Professor of Diabetic Medicine, Division of Diabetes and Nutritional Sciences, King's College London, London, UK

Pablo Aschner, Associate Professor of Endocrinology, Javeriana University School of Medicine, Director of Research, San Ignacio University Hospital, and Scientific Director of the Colombian Diabetes Association, Bogotá, Colombia

Belinda Childs, RN, Executive Director, Clinical Nurse Specialist, Great Plains Diabetes, Wichita, KS Philip E. Cryer, Professor of Medicine Emeritus, Washington University in St. Louis, St. Louis, MO Bastiaan E. de Galan, Department of Internal Medicine, Radboud University Niimegen Medical Centre, Nijmegen, the Netherlands

Simon R. Heller, Professor of Clinical Diabetes, University of Sheffield, and Director of Research and Development and Honorary Consultant Physician, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK

Brian M. Frier, Honorary Professor of Diabetes, The Queen's Medical Research Institute, University of Edinburgh, Edinburgh, Scotland, UK Linda Gonder-Frederick, Associate Professor, Department of Psychiatry and Neurobehavioral Sciences, and Clinical Director, Behavioral Medicine Center, University of Virginia Health System, Charlottesville, VA, USA

Timothy Jones, Clinical Professor, School of Paediatrics and Child Health, Telethon Institute for Child Health Research, University of Western Australia, and Head, Department of Endocrinology and Diabetes, Princess Margaret Hospital for Children, Perth, WA, Australia

Kamlesh Khunti, Professor of Primary Care Diabetes and Vascular Medicine, University of Leicester, Leicester, UK

Lawrence A. Leiter. Division of Endocrinology and Metabolism, St. Michael's Hospital and Professor of Medicine and Nutritional Sciences, University of Toronto, Toronto, ON, Canada Rory J. McCrimmon, Professor of Experimental Diabetes and Metabolism, Division of Molecular & Clinical Medicine, School of Medicine, University of Dundee, Dundee, Scotland, UK Yingying Luo, Associate Professor, Endocrinology

People's Hospital, Beijing, China Elizabeth R. Seaguist. Pennock Family Chair in Diabetes Research, Professor of Medicine, and Director, Division of Endocrinology and Diabetes, Department of Medicine, University of

and Metabolism Department, Peking University

Minnesota, Minneapolis, MN, USA Robert Vigersky, Medical Director, Medtronic Diabetes, Washington, DC, and Professor of Medicine, Uniformed Services University of the Health Sciences, Bethesda, MD, USA

Sophia Zoungas, Professor of Diabetes, Vascular Health and Ageing, School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC, Australia

References

- 1. Amiel SA, Sherwin RS, Simonson DC, Tamborlane WV. Effect of intensive insulin therapy on glycemic thresholds for counterregulatory hormone release. Diabetes 1988;37: 901-907
- 2. Boyle PJ, Schwartz NS, Shah SD, Clutter WE, Cryer PE. Plasma glucose concentrations at the onset of hypoglycemic symptoms in patients with poorly controlled diabetes and in nondiabetics. N Engl J Med 1988;318:1487-1492
- 3. Heller SR, Cryer PE. Reduced neuroendocrine and symptomatic responses to subsequent hypoglycemia after 1 episode of hypoglycemia in nondiabetic humans. Diabetes 1991;40: 223-226

- 4. Dagogo-Jack SE, Craft S, Cryer PE. Hypoglycemiaassociated autonomic failure in insulin-dependent diabetes mellitus. Recent antecedent hypoglycemia reduces autonomic responses to, symptoms of, and defense against subsequent hypoglycemia. J Clin Invest 1993;91: 819-828
- 5. Crver PE. Mechanisms of hypoglycemiaassociated autonomic failure in diabetes. N Engl J Med 2013;369:362-372
- 6. Workgroup on Hypoglycemia, American Diabetes Association. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. Diabetes Care 2005;28:1245-1249
- 7. Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and The Endocrine Society. Diabetes Care 2013:36:1384-1395
- 8. Cryer PE. The prevention and correction of hypoglycemia. In Handbook of Physiology, Section 7. Volume II. The Endocrine Pancreas and Regulation of Metabolism. Jefferson LS, Cherrington AD, Eds. New York, Oxford University Press, 2001, p. 1057-1092
- 9. Cryer PE. *Hypoglycemia in Diabetes*. 3rd ed. Alexandria, VA, American Diabetes Association,
- 10. Frier BM, Heller SR, McCrimmon RJ, Eds. Hypoalycaemia in Clinical Diabetes, 3rd ed. Chichester, U.K., John Wiley & Sons, 2014, p. 49 11. Heller SR, Macdonald IA. The measurement of cognitive function during acute hypoglycaemia: experimental limitations and their effect on the study of hypoglycaemia unawareness. Diabet Med 1996;13:607-615
- 12. Choudhary P, Lonnen K, Emery CJ, et al. Comparing hormonal and symptomatic responses to experimental hypoglycaemia in insulin- and sulphonylurea-treated type 2 diabetes. Diabet Med 2009;26:665-672
- 13. Matyka K, Evans M, Lomas J, Cranston I, Macdonald I, Amiel SA. Altered hierarchy of protective responses against severe hypoglycemia in normal aging in healthy men. Diabetes Care 1997:20:135-141
- 14. Gonder-Frederick LA, Zrebiec JF, Bauchowitz AU, et al. Cognitive function is disrupted by both

- hypo- and hyperglycemia in school-aged children with type 1 diabetes: a field study. Diabetes Care 2009;32:1001-1006
- 15. Fanelli CG, Epifano L, Rambotti AM, et al. Meticulous prevention of hypoglycemia normalizes the glycemic thresholds and magnitude of most of neuroendocrine responses to, symptoms of, and cognitive function during hypoglycemia in intensively treated patients with short-term IDDM. Diabetes 1993;42:1683-1689 16. Fanelli C, Pampanelli S, Epifano L, et al. Long-term recovery from unawareness, deficient counterregulation and lack of cognitive dysfunction during hypoglycaemia, following institution of rational, intensive insulin therapy in IDDM. Diabetologia 1994:37:1265-1276
- 17. Cranston I, Lomas J, Maran A, Macdonald I, Amiel SA. Restoration of hypoglycemia awareness in patients with long-duration insulindependent diabetes. Lancet 1994;344:283:287 18. Dagogo-Jack S. Rattarasarn C. Crver PE. Reversal of hypoglycemia unawareness, but not defective glucose counterregulation, in IDDM. Diabetes 1994:43:1426-1434
- 19. Chow E, Bernjak A, Williams S, et al. Risk of cardiac arrhythmias during hypoglycemia in patients with type 2 diabetes and cardiovascular risk. Diabetes 2014;63:1738-1747
- 20. Pistrosch F, Ganz X, Bornstein SR, Birkenfeld AL, Henkel E, Hanefeld M. Risk of and risk factors for hypoglycemia and associated arrhythmias in patients with type 2 diabetes and cardiovascular disease: a cohort study under real-world conditions. Acta Diabetol 2015;52:889-895
- 21. Bonds DE, Miller ME, Bergenstal RM, et al. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. BMJ 2010;340:b4909
- 22. ORIGIN Trial Investigators, Mellbin LG, Rydén L, Riddle MC, et al. Does hypoglycaemia increase the risk of cardiovascular events? A report from the ORIGIN trial. Eur Heart J 2013;34:3137-3144 23. Finfer S, Liu B, Chittock DR, et al.; NICE-SUGAR Study Investigators. Hypoglycemia and risk of death in critically ill patients. N Engl J Med 2012;367:1108-1118
- 24. International Hypoglycaemia Study Group. Minimizing hypoglycemia in diabetes. Diabetes Care 2015;38:1583-1591