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Glucose concentrations of less than 3.0 mmol/l (54 mg/dl) should be reported in clinical trials

International Hypoglycaemia Study Group

Published in:
Diabetologia

DOI:
[10.1007/s00125-016-4146-6](https://doi.org/10.1007/s00125-016-4146-6)

Publication date:
2016

Licence:
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Document Version
Publisher's PDF, also known as Version of record

[Link to publication in Discovery Research Portal](#)

Citation for published version (APA):

International Hypoglycaemia Study Group (2016). 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. *Diabetologia*. <https://doi.org/10.1007/s00125-016-4146-6>

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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

The International Hypoglycaemia Study Group

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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 hypoglycaemia, be included in reports of clinical trials of glucose-lowering drugs evaluated for the treatment of diabetes mellitus.

The glycaemic thresholds for symptoms of hypoglycaemia and for glucose counterregulatory (including sympathoadrenal) responses to hypoglycaemia, 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 glycaemic control and at lower glucose concentrations in those with tight glycaemic control [1–5]. The shifts in glycaemic threshold to lower glucose concentrations are largely the result of more frequent episodes of iatrogenic hypoglycaemia during intensive glycaemic therapy. Glycaemic thresholds for responses to hypoglycaemia vary, not only among individuals with diabetes but also in the same

individual with diabetes as a function of their HbA_{1c} levels and hypoglycaemic experience; it is therefore not appropriate to cite a specific glucose concentration that defines hypoglycaemia in diabetes. As a consequence, the American Diabetes Association has defined hypoglycaemia in diabetes non-numerically 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 hypoglycaemia 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 hypoglycaemia, 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 min) or a laboratory measurement of plasma glucose. Both of these levels are distinctly low glucose concentrations that do not occur under physiological conditions in non-diabetic individuals [8]. Thus, they are unequivocally hypoglycaemic values. They approximate the upper and lower limits, respectively, of the non-diabetic

Members of the International Hypoglycaemia Study Group are listed in the [Appendix](#).

Simultaneous publication: 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.

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glycaemic threshold for symptoms of insulin-induced hypoglycaemia [8–10]. The generic non-diabetic glycaemic threshold for impairment of cognitive function is <2.8 mmol/l [8–10], but higher glucose levels have been reported for some tests [11–14]. Glucose concentrations of both <3.0 mmol/l and <2.8 mmol/l cause defective glucose counterregulation and impaired awareness of hypoglycaemia, the core components of hypoglycaemia-associated autonomic failure in diabetes [5]. Avoiding these glucose levels could reverse impaired awareness of hypoglycaemia [15–18] and some aspects of defective glucose counterregulation [15–17] in many affected patients. In type 1 diabetes, failure to recognise one's own hypoglycaemia at a glucose concentration <3.0 mmol/l increased the risk of severe hypoglycaemia (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 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 Outcomes 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 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 hypoglycaemia. Possible terms used to describe this condition include 'serious', 'clinically important', 'major' or 'clinically significant'. The group decided not to describe 'severe hypoglycaemia' in terms of glucose concentration since there is currently widespread agreement that severe hypoglycaemia, 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 hypoglycaemic risk (text box).

Proposed glucose levels when reporting hypoglycaemia 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

Level 2

A glucose level of <3.0 mmol/l (<54 mg/dl) is sufficiently low to indicate serious, clinically important hypoglycaemia

Level 3

Severe hypoglycaemia, as defined by the ADA [6,7], denotes severe cognitive impairment requiring external assistance for recovery

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, ON, 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 hypoglycaemia is an under-recognised problem that deserves increased awareness and focus across the healthcare community. The group's ultimate goal is to improve the lives of patients with diabetes.

Duality of Interest PA 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. BC has had research grant support from Halozyme and Lilly to the former MidAmerica Diabetes Associates. PEC has served on scientific advisory boards for Novo Nordisk. BEdG has served on scientific advisory boards for Novo Nordisk and Sanofi and received research grant support from AstraZeneca. SRH 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 UK Ltd. BMF has served on scientific advisory boards and as a speaker for Boehringer Ingelheim, Janssen, Merck Sharp & Dohme, Novo Nordisk and Lilly. LG-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. TJ has served as a speaker for Novo Nordisk, Lilly, Medtronic and Sanofi. KK 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. LAL 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. RJM has served on scientific advisory boards for Novo Nordisk and Sanofi. ERS has undertaken consultancy for Sanofi, Novo Nordisk, Lilly, Locemia and Medtronic and received grant support from Lilly. RV is an employee and owns stock in Medtronic Inc. SZ 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

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