The Association of Biochemical Hypoglycemia with the Subsequent Risk of a Severe Hypoglycemic Event: Analysis of the DCCT Data Set

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Abstract

Objective: To evaluate the association of biochemical hypoglycemia with subsequent severe hypoglycemia (SH) events using the Diabetes Control and Complications Trial (DCCT) data set.

Research Design and Methods: The frequency of biochemical hypoglycemia (percentage of values <70 and <54 mg/dL [3.9 and 3.0 mmol/L]) was assessed using DCCT blood glucose concentrations measured at a central laboratory from seven finger-stick samples (7-point testing: pre- and 90-min postmeals and at bedtime) collected during 1 day every 3 months. SH events required a change in mental status necessitating the involvement of another individual to provide treatment. A Poisson model accounting for repeated measures from each participant was used to assess the association of biochemical hypoglycemia frequency, computed from the 7-point finger-stick data, with the development of SH events.

Results: The risk of SH during a 3-month period was substantially higher ($P < 0.001$) when there was at least one hypoglycemic blood glucose value in the preceding 7-point profile, with similar results seen for both the 70 mg/dL (rate ratio = 3.0 [95% confidence interval: 2.6–3.3]) and 54 mg/dL (rate ratio = 2.7 [95% confidence interval: 2.4–3.1]) thresholds.

Conclusions: The occurrence of biochemical hypoglycemia <70 or <54 mg/dL is associated with an increased risk of SH. For this reason as well as the deleterious effects of hypoglycemia on glucose counter-regulation and hypoglycemia awareness, cognition, quality of life, and arrhythmias, it is important in diabetes management to avoid hypoglycemic glucose levels as much as possible.

Keywords: Severe hypoglycemia, Biochemical hypoglycemia, Risk assessment, Type 1 diabetes.

Introduction

TO OPTIMIZE DIABETES MANAGEMENT, it is essential to have assessments of both hyperglycemia and hypoglycemia. HbA1c is primarily a measure of hyperglycemia, but it provides no indication of the frequency or severity of hypoglycemia. However, combining HbA1c with continuous glucose monitoring (CGM) provides not only measures of hypoglycemia and hyperglycemia but also information about the patterns of glycemia over the course of the day. Recently, several organizations have published consensus statements that included the specific CGM metrics to report for hypoglycemia: time <54 mg/dL and time <70 mg/dL.^{1–3} Sub-

stantial evidence exists to provide clinical validation of biochemical hypoglycemia such as time <54 mg/dL as a clinically relevant outcome, including the association of biochemical hypoglycemia with the subsequent occurrence of a severe hypoglycemia (SH) event.⁴ However, the Food and Drug Administration has been hesitant to accept CGM-measured outcomes as measures of hypoglycemia efficacy or safety for a drug or device and has required that a study demonstrates a reduction in SH events for efficacy. This limits the feasibility of clinical trials to demonstrate a beneficial effect on hypoglycemia since the rate of SH events during a reasonable study time frame is quite low, unless the study cohort is limited to a population at high risk for SH.⁵

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In the Diabetes Control and Complications Trial (DCCT), the SH rate was substantially higher than has been demonstrated in recent studies.⁶ As a result, the DCCT data set is useful to evaluate factors associated with SH. During the DCCT, participants were asked to collect a blood sample seven times a day once every 3 months for blood glucose measurement by a central laboratory (referred to as “7-point testing”). These data, although sparse compared with the 288 daily data points obtained with CGM, nevertheless provided the opportunity to evaluate the association of biochemical hypoglycemia and subsequent SH.

Methods

Public DCCT data sets were obtained from the National Institute of Diabetes and Digestive and Kidney Disease Central Database Repository, and with the assistance of the Biostatistics Center at George Washington University. An Institutional Review Board waiver was received to conduct the analyses. The DCCT methods and cohort characteristics have been well described in many publications and are not repeated here.^{6,7}

The analyses used data collected during the DCCT (1983–1993). Glycemic data used in the analyses included (1) the quarterly 7-point glucose measurements and (2) recorded SH events. The 7-point testing consisted of blood samples collected in capillary tubes pre- and 90 min postmeals and at bedtime that were sent to the central laboratory at the University of Minnesota for glucose measurement. The DCCT definition of SH was an episode with symptoms or signs consistent with hypoglycemia in which the individual required the assistance of another person (e.g., as a result of confusion, coma, or seizure) and which was associated with a blood glucose level <50 mg/dL or prompt recovery after administration of oral carbohydrate, glucagon, or intravenous glucose.

The degree of completeness of the 7-point testing data has been reported.⁸ Among the 1441 DCCT participants, quarterly blood glucose testing was performed on 32,534 occasions. Only the 30,586 profiles with at least six glucose measurements (5689 [19%] with six measurements and 24,897 [81%] with seven measurements, referred to as 7-point testing even if only six measurements were performed) and the ensuing 3-month periods to assess SH were included in the analyses. Among the 3782 SH events reported during DCCT, 3440 occurred during a 3-month period for which preceding analyzable 7-point testing data were available.

For each 7-point testing day, the frequency of values <70 and <54 mg/dL was computed. A Poisson model accounting for repeated measures from each participant was used to assess the association of biochemical hypoglycemia frequency, computed from the 7-point glucose data, with the development of SH events and to compute rate ratios with 95% confidence intervals. Since Poisson models are sensitive to outliers, the number of SH events was truncated at three. Modeling using the nontruncated number of SH events produced a similar result.

Analyses were performed using SAS 9.4 software (SAS Institute, Inc., Cary, NC).

Results

At least one SH event occurred in 673 (47%) of the 1441 participants, with 198 (14%) experiencing one event, 226

(16%) two to four events, and 249 (17%) five or more events (Table 1). At least one SH event occurred during 2201 (7%) of the 30,586 three-month periods preceded by a 7-point blood glucose profile. Among the 2201 three-month periods with at least one SH event, 1644 (75%) periods had one SH event, 353 (16%) had two events, 115 (5%) had three events, 52 (2%) had four events, 19 (0.9%) had five events, and 18 (0.8%) had six or more events. At least one glucose value <70 mg/dL was present in 12,401 (41%) of the 30,586 profiles and at least one value <54 mg/dL in 5213 (17%) profiles (Table 2).

The risk of SH during a 3-month period was substantially higher ($P < 0.001$) when there was at least one hypoglycemic blood glucose value in the preceding 7-point profile (Table 3, Fig. 1), with similar results seen for both the 70 and 54 mg/dL thresholds. The rate ratios for an SH event during the 3-month period were 3.0 (95% confidence interval: 2.6–3.3) and 2.7 (95% confidence interval: 2.4–3.1), respectively, for one or more values <70 or <54 mg/dL compared with no hypoglycemic values in the preceding 7-point profile. The risk of an SH event increased more than threefold when at least four values in a profile were in the hypoglycemic range.

The relationship between the presence of hypoglycemia in a 7-point profile and subsequent SH was seen in both treatment groups ($P < 0.001$ within each treatment group for both <70 and <54 mg/dL) (Table 3). In the intensive treatment group, the rate ratio for an SH event during the 3-month period was 1.9 (95% confidence interval: 1.7–2.1) and 1.8 (95% confidence interval: 1.6–2.1) for one or more values <70 or <54 mg/dL compared with no hypoglycemic values in the preceding 7-point profile, and in the standard treatment group the rate ratios were 3.4 (95% confidence interval: 2.7–4.3) and 4.1 (95% confidence interval: 3.3–5.2), respectively.

Discussion

The landmark DCCT data set has proven useful for addressing a wide range of clinically important questions. In a

TABLE 1. DISTRIBUTION OF NUMBER OF SEVERE HYPOGLYCEMIA EVENTS PER SUBJECT (N = 1441 SUBJECTS)

Number of events	During 3-month periods following blood glucose profiles (includes 3440 events)		During all DCCT (includes 3782 events)	
	Frequency	Percent	Frequency	Percent
0	768	53	727	50
1	198	14	210	15
2	96	7	104	7
3	80	6	78	5
4	50	3	59	4
5	50	3	49	3
6	40	3	36	2
7	24	2	21	1
8	21	1	18	1
9	20	1	21	1
10	12	<1	19	1
11–20	62	4	75	5
≥21	20	1	24	2

DCCT, Diabetes Control and Complications Trial.

TABLE 2. DISTRIBUTION OF THE NUMBER OF BLOOD GLUCOSE VALUES <70 AND <54 mg/dL IN 7-POINT PROFILES (N=30,586 PROFILES)

Number below threshold	<70 mg/dL		<54 mg/dL	
	Frequency	Percent	Frequency	Percent
0	18,185	59	25,373	83
1	7608	25	4089	13
2	3228	11	893	3
3	1103	4	173	<1
4	331	1	41	<1
5	86	<1	11	<1
6	31	<1	4	<1
7	14	<1	2	<1

prior publication, using the DCCT data set we reported a strong association between time in range of 70–180 mg/dL, measured with 7-point blood glucose testing, and the development of retinopathy and microalbuminuria.⁹ In this study, we used the DCCT data set to assess the association of biochemical hypoglycemia assessed 1 day each quarter with the occurrence of an SH event during the ensuing 3 months. The risk of an SH event during the 3-month period was more than twofold greater when there was at least one hypoglycemic blood glucose measurement on the 7-point testing, and risk increased further when there was more than one hypoglycemic blood glucose concentration. Results were similar for both the <70 and <54 mg/dL hypoglycemia thresholds, which is not surprising since time <70 mg/dL and time <54 mg/dL have been shown to be highly correlated (and time <70 mg/dL includes time <54 mg/dL.¹⁰ The risk of SH was substantially higher in the intensive versus standard care treatment groups but the pattern of association of biochemical hypoglycemia with subsequent SH was similar between groups.

The study results are consistent with the findings of the Juvenile Diabetes Research Foundation CGM randomized control trial, which showed that CGM-measured hypoglycemia on one day was strongly associated ($P<0.001$) with the occurrence of an SH event on the following day.¹¹ The SH risk was >10 times higher when the glucose concentration was ≤ 70 mg/dL for >30% of the time on the prior day compared with $\leq 5\%$ of the prior day. The occurrence of at least 30 consecutive minutes ≤ 54 mg/dL on one day increased the SH risk on the following day by more than two times. The study results also are consistent with the results by Kovatchev et al. who showed in one study that hypoglycemia measured with a blood glucose meter for a month was associated with SH risk in the subsequent 6 months,¹² and in another study that blood glucose meter hypoglycemia was higher in the 24 h before an SH event than on other days.¹³ Cox et al. also has demonstrated that association between meter-measured hypoglycemia and subsequent SH.¹⁴ Although in this study and in prior studies, the association between biochemical hypoglycemia and a subsequent SH event is very strong, the predictive value is low due to the relatively low frequency of SH events.

Prevention of hypoglycemia <70 and <54 mg/dL should be a goal of diabetes management.^{4,15} Preventing levels <70 mg/dL is important as glucose levels dropping into the 60s are strongly associated with lower glucose levels. Preventing levels <54 mg/dL is particularly important since, in addition to the increased risk of an SH event as has been demonstrated in this and the other studies already cited, there are a number of deleterious effects when the glucose concentration drops this low. This includes the development of impaired glucose counter-regulation and reduced hypoglycemia awareness,^{16–18} which has been associated with an increased risk of severe clinical hypoglycemic events¹⁹; cognitive function impairment^{20–23}; an

TABLE 3. NUMBER OF SEVERE HYPOGLYCEMIA EVENTS IN SUBSEQUENT 3 MONTHS ACCORDING TO NUMBER OF BLOOD GLUCOSE MEASUREMENTS <70 AND <54 mg/dL (N=30,586 PROFILES)

Number below threshold	<70 mg/dL			<54 mg/dL		
	n	Mean number of SH events in next 3M	≥ 1 SH events in next 3M	n	Mean number of SH events in next 3M	≥ 1 SH events in next 3M
Treatment groups combined (n=1441)						
0	18,185	0.06	4%	25,373	0.08	6%
1	7608	0.14	10%	4089	0.21	14%
2	3228	0.20	14%	893	0.24	15%
3	1103	0.24	15%	173	0.29	17%
≥ 4	462	0.24	14%	58	0.22	16%
Intensive treatment group (n=711)						
0	6618	0.11	8%	11,337	0.13	10%
1	4904	0.18	12%	2894	0.24	16%
2	2354	0.23	15%	687	0.25	17%
≥ 3	1202	0.26	16%	160	0.34	20%
Standard treatment group (n=730)						
0	11,567	0.03	2%	14,036	0.03	3%
1	2704	0.07	5%	1195	0.13	10%
2	874	0.13	9%	206	0.20	11%
≥ 3	363	0.16	10%	71	0.11	10%

$P<0.001$ for both <70 mg/dL and <54 mg/dL overall and within each treatment group from Poisson models accounting for repeated measures from each participant.

SH, severe hypoglycemia.

FIG. 1. Frequency of ≥ 1 SH event in a 3-month period according to the number of hypoglycemia blood glucose values in the preceding profile. SH, severe hypoglycemia.

increase in cardiac arrhythmias (mortality)^{24–29}; an adverse effect on quality of life, including sleep^{30–34}; reduced work productivity^{35,36}; and impaired driving with an increase in car accidents.^{37–39}

The strengths of the study include the use of the DCCT data that were meticulously collected to record SH events using a standardized definition. However, there are certain limitations inherent in using 7-point testing data compared with CGM data. First, the data represent only seven measurements during 1 day compared with up to 288 with CGM and does not include overnight measurements. Although there is a benefit in having a structured testing schedule to avoid bias, this also means that instances of hypoglycemia on the testing day may have been missed. Second, having only 1 day of measurements every 3 months limits the ability to assess a close temporal relationship between the 7-point measured hypoglycemia and SH. Despite these limitations, a strong association was demonstrated between biochemical hypoglycemia and SH. Presumably for many participants, the frequency of hypoglycemia in the 7-point data on 1 day is reasonably reflective of the frequency of biochemical hypoglycemia throughout the 3-month period. It is possible that with more frequent glucose measurements as would be present with CGM, the association between biochemical hypoglycemia and SH events could be even stronger than what was found in this study.

In summary, this study using the DCCT data set affirms the findings of other studies that the occurrence of biochemical hypoglycemia <70 or <54 mg/dL is associated with an increased risk of SH. For this reason as well as the deleterious effects of hypoglycemia on glucose counter-regulation and hypoglycemia awareness, cognition, quality of life, and arrhythmias, it is important in diabetes management to avoid hypoglycemic glucose levels as much as possible. The evidence from this study and prior studies is substantial and the case compelling for regulators to accept biochemical hypoglycemia, measured with CGM, as a meaningful endpoint for clinical trials.

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Authors' Contributions

R.W.B. wrote the article, R.M.B. contributed to and reviewed/edited the article, and T.D.R. and C.K. performed statistical analyses and reviewed/edited the article.

Author Disclosure Statement

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