Type 1 diabetic drivers with and without a history of recurrent hypoglycemia-related driving mishaps: Physiological and performance differences during euglycemia and the induction of hypoglycemia

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**Objective:** Collisions are more common among drivers with type 1 diabetes than non-diabetic spouses. This increased risk appears to be attributable to a subgroup of drivers with type 1 diabetes. The hypothesis tested is that this vulnerable subgroup is more at-risk for hypoglycemia and its disruptive effects on driving.

**Research Design and Methods:** Thirty-eight drivers with type 1 diabetes, 16 with (+History) and 22 without (-History) a recent history of recurrent hypoglycemia-related driving mishaps, drove a virtual reality driving simulator and watched a videotape of someone driving a simulator for 30-minute periods. Driving and video testing occurred in a double-blind, randomized, cross-over manner during euglycemia (5.5 mmol/L) and progressive hypoglycemia (3.9 to 2.5 mmol/L). Examiners were blind to which subjects were +/-History, while subjects were blind to their blood glucose levels and targets.

**Results:** During euglycemia, +History participants reported more autonomic and neuroglycopenic symptoms ($p<.01$) and tended to require more dextrose infusion to maintain euglycemia with the same insulin infusion ($p<.09$). During progressive hypoglycemia, these subjects demonstrated less epinephrine release ($p=.02$) and greater driving impairments ($p=.03$).

**Conclusions:** Findings support the speculation that there is a subgroup of type 1 diabetes drivers more vulnerable to experiencing hypoglycemia-related driving mishaps. This increased vulnerability may be due to more symptom "noise" (more symptoms during euglycemia), making it harder to detect hypoglycemia while driving; possibly greater carbohydrate utilization, rendering them more vulnerable to experiencing hypoglycemia; less hormonal counter-regulation, leading to more profound hypoglycemia; and more neuroglycopenia, rendering them more vulnerable to impaired driving.

**Worldwide driving collisions** account for 1.2 million fatalities and 50 million injuries annually. [1] Drivers with type 1 diabetes have more driving mishaps [2]; in both Europe and the United States type 1 drivers have been found to have more than twice as many collisions than their non-diabetic spouses. [3] This may be because mild hypoglycemia significantly impacts cognitive–motor functioning in general, [4, 5, 6] and the cognitive-motor skills relevant to driving a car in particular. [7, 8] Severe hypoglycemia precludes safe driving and can contribute to vehicular fatalities. [9] Further, mild hypoglycemia can impair judgment as to whether or not to drive. [10, 11] Just as some individuals with type 1 diabetes are more vulnerable to experiencing severe hypoglycemia, [12] some individuals may be more vulnerable to hypoglycemia-related driving mishaps. This speculation is supported by the U.S.-Europe survey [3] where only 27% of the type 1 diabetes drivers reported vehicular collisions in the previous two years, [3] and a prospective study where only 22% of the sample reported a collision during the 12 month observation. [13] In a previous study of hypoglycemia and driving, we conducted *post hoc* analyses comparing individuals with a recent...
history of no driving mishaps versus individuals with a history of multiple driving mishaps. [14] Those with a +History were more likely to be female (p=.02), trended to demonstrate greater carbohydrate utilization (p=.07) and less epinephrine release (p=.11), and drove significantly worse during hypoglycemia (p=.01). [14] The present study was an a priori hypothesis-testing replication comparing subjects with or without a recent history of recurrent hypoglycemia-related driving mishaps, employing a similar methodology, to test whether +History type 1 diabetes drivers were: 1) more vulnerable to experiencing hypoglycemia through greater carbohydrate utilization, 2) more likely to be female, 3) more vulnerable to progressive hypoglycemia due to a smaller counter regulatory epinephrine response , 4) less aware of hypoglycemia due to fewer symptoms (autonomic and neuroglycopenic) during hypoglycemia, and 5) more impaired while driving during hypoglycemia.

RESEARCH DESIGN AND METHODS

Subjects: Forty-two adults with type1 diabetes were recruited through regional advertisements. Inclusion criteria were that subjects: 1) had type 1 diabetes for at least one year, 2) were between the ages of 21 and 70, 3) drove a minimum of 6,000 miles a year, and 4) either reported no driving mishaps (no collisions, citations, automatic driving where they drove from point A to B with no recollection, or someone else took over control of the vehicle due to hypoglycemia) in the past 12 months (+History group), or reported at least two such mishaps in the past 12 months (-History group). Further, because we were going to expose subjects to hypoglycemia (~2.2 mmol/L) through insulin infusion and take frequent blood samples, we excluded subjects with hematocrit <38% for males or <36% for females, presence of an electronic pacemaker or more than 5% atrial or ventricular ectopy, and pregnant females. Four subjects prematurely discontinued testing: three had insufficient IV access for the hyperinsulinemic clamp procedure and one experienced lower extremity muscle twitching resulting from acute or chronic hypomagnesemia. The resulting sample of 38 participants had a mean age of 42.5 ± 12 yrs (Median =42, range 21-66 years), disease duration of 21.6 ± 9.4yrs (Median =20, range 1-52 years), and HbA1c of 7.4 ± 0.8%. As illustrated in Table 1, the +/-History groups did not differ on any diabetes, hypoglycemia or driving parameters other than +History subjects reported more episodes of severe hypoglycemia and driving mishaps in the previous 12 months.

Procedure: After signing an IRB-approved consent form, participants completed an outpatient screening evaluation including a medical history, physical examination, 12 lead EKG’s, and laboratory evaluations with HbA1c, complete blood count, and comprehensive metabolic panel. They were also introduced to and rehearsed using the simulator. For the 48 hours prior to admission, subjects were instructed to avoid hypoglycemia by reducing total insulin by 10%, routinely testing BG five times a day, and eating prophylactically 10g of carbohydrates when BG fell <5.5 mmol/L. Intermediate and long-acting insulins were discontinued 24 and 36 hours prior to hospitalization, respectively. During this pre-admission period and hospital admission, only short and rapid-acting insulins were used.
Subjects were admitted to the University of Virginia General Clinical Research Center at 4 PM on the evening prior to the hyperinsulinemic clamping procedure. Subjects were instructed on and given time to again practice driving the simulator and rating nine common symptoms of hypoglycemia on a 0-6 scale into a hand held computer. Subjects were then provided with a standardized (50% carbohydrate, 20% protein and 30% fat) eucaloric, caffeine-free meal at 6 PM and a bedtime snack at 9 PM. Subjects were allowed glucose-free, caffeine-free drinks throughout the evening, and retired at 11 PM. Subjects were not allowed to eat any additional food during hospitalization other than that provided by the GCRC or that required to treat BG < 5.5 mmol/L. Two IV lines were placed in the non-dominant hand and arm for overnight infusion of insulin and hourly blood sampling to maintain glucose between 5.6 and 8.3 mmol/L.

On the first morning of testing, subjects were awakened at ~7 AM and given time to freshen up. They remained fasting until after the study procedures were completed. Immediately before testing, an additional retrograde hand IV was inserted. Activated charcoal packets were affixed over this IV area for arterialized sampling of BG every five minutes and epinephrine every 10 minutes. [15] Euglycemia, with a plasma glucose goal of 6.1 mmol/L (110 mg/dl), was achieved and maintained using variable 20% dextrose infusion. [16] After glucose and insulin stabilization, subjects performed 30-minutes of testing. Subsequently dextrose infusion was slowed or discontinued to ensure a steady descent into hypoglycemia at a BG rate of fall of 0.055 mmol/L/min. Progressive hypoglycemia testing began when BG reached 3.9 mmol/L (70 mg/dl) and ended 30 minutes later at a BG nadir of 2.5 mmol/L (45 mg/dl). [16] Progressive hypoglycemia, rather than the traditional hypoglycemia clamp, [4, 5] was employed because it was thought to be more similar to real-world conditions. Euglycemia testing always preceded hypoglycemia testing to avoid any lingering neuroglycopenia impacting performance during euglycemia. The second day of testing followed the same procedures. Testing was done on two consecutive days to avoid losing subjects due to rescheduling a second hospitalization. Figure 1 depicts the randomized cross-over research design. Hypoglycemic driving was equally as likely to occur on day one or two among +/-Hypoglycemia subjects, thus negating any antecedent hypoglycemia or practice effect impacting on a Group effect.

During the testing periods, subjects either drove the simulator or sat in the simulator and watched a videotape of someone else driving a simulator. At 0, 10, 20, and 30 minutes into testing, subjects rated four autonomic symptoms (sweatiness, pounding heart, jittery/tension, trembling) and five neuroglycopenic symptoms (uncoordination, visual difficulty, lightheadedness, difficulty concentrating, confusion) on a 0 (not at all) to 6 (extremely) scale. If subjects believed they were experiencing low BG anytime during testing they were instructed to self-treat with an orange drink (sugar free placebo).

Subjects were told their BG was going to be raised and lowered for testing throughout the study but were kept blind to their actual BG and targeted BG levels. Researchers conducting the testing were kept blind to whether subjects had or did not have a recent history of hypoglycemia-related driving mishaps.
The Atari Research Driving Simulator is an interactive, fixed-platform, virtual reality simulator that generates reliable, accurate, sensitive, and valid driving performance data. [7, 8, 18, 20-22] The simulator has three 25-inch computer screens that provide a 160-degree visual field, along with a programmed rear-view mirror depicting rear traffic. The driving environment is realistic, incorporating a typical-sized steering wheel, gas and brake pedals, seat, and seat belt. Driving performance feedback is provided visually through the three screens that update at a rate of 60 times per second; audibly through quadraphonic speakers delivering engine, tire, and road noises; and kinesthetically through forced feedback from the steering wheel and pedal pressure. The simulator records three steering variables (standard deviation of lane position, driving off road, and veering across the midline); three braking variables (inappropriate braking while on the open road, missed stopped signals, and collisions); and four speed control variables (exceeding speed limit, standard deviation of speed, time at stop sign deciding when to turn left, and time to execute a left turn).

**Outcome Variables:** Using DeFronzo’s algorithm, [17] individual’s metabolic demand was determined and reported as glucose utilization rates in mg/kg/min. Plasma epinephrine was measured using a single isotope derivative method. [15]

As in previous studies that discriminated high-risk subjects and predicted future driving collisions, [7, 8, 14, 18, 20-22] we generated and analyzed a composite Impaired Driving Score (IDS) to compare the various aspects of driving poorly. To compute the IDS, a subject’s performance on each variable (e.g. standard deviation of speed) was converted into a z-score based on all subjects’ performances on that variable during euglycemia and hypoglycemia. The z-scores for all variables were then summed for each subject from each test drive, generating the IDS. Thus, an IDS of 0 represents average driving, an IDS less than 0 represents better than average driving (e.g. an IDS of -1 represents driving performance 1 SD per variable better than average), and an IDS greater than 0 represents worse than average driving.

To evaluate whether +History subjects differed from -History subjects across two euglycemia and hypoglycemia, 2 Between (Group) X 2 Within (Conditions) repeated measure ANCOVA’s were performed, with subject’s average BG for that condition used as the covariate.

**RESULTS**

**Carbohydrate utilization:** +History subjects demonstrated a trend toward greater carbohydrate utilization (F=3.064, p=0.089). +History subjects demonstrated a 16.1% greater carbohydrate utilization to maintain euglycemia than -History subjects.

**Driving performance:** While +History subjects drove just as well as -History during euglycemia, they demonstrated a marked impairment in performance during progressive hypoglycemia (Group X Condition F=5.0, p=.03). As illustrated in Figure 2, +History subjects’ driving performance worsened almost 2.5 standard deviations from euglycemia to hypoglycemia, while –History subjects demonstrated no driving impairment, driving slightly (but not significantly) better during hypoglycemia.

**Epinephrine response:** Peak epinephrine released was greater during hypoglycemia than during euglycemic condition (Condition F=57.35, p<.0001), and +History subjects released less
epinephrine during hypoglycemia (Group X Condition F=6.05, p=.02). However, post hoc analyses of peak epinephrine response during hypoglycemia (Gender X Group F=2.938, p=.097) indicates this reduced epinephrine response by +History subjects was primarily due to females, with mean peak epinephrine for male and female – History and male +History subjects was 382, 329 and 316 pg/ml respectively, but 168 pg/ml for female +History subjects.

**Symptom Perception:** +History subjects reported more autonomic symptoms than -History subjects (F=7.79, p=.009), with a near significant interaction (F=3.95, p=.055). As seen in Figure 3, +History subjects tended to report more symptoms during euglycemia than hypoglycemia, while -History subjects demonstrated the anticipated increase in autonomic symptoms during hypoglycemia. Neuroglycopenic symptoms followed a similar pattern: +History subjects tended to report more neuroglycopenic symptoms than -History subjects (Group F=2.9, p=.09), with a significant interaction (F=4.00, p=.05). Figure 3 illustrates that +History subjects reported more neuroglycopenic symptoms during euglycemia than hypoglycemia, while -History subjects demonstrated the anticipated increase in perceived neuroglycopenic symptoms with hypoglycemia. Contrasts indicated that +History subjects reported more autonomic (p<.001) and neuroglycopenic (p=.018) symptoms during euglycemia than -History subjects.

Assuming that hypoglycemic symptom perception in part contributes to self-treatment, self-treatment and symptom perception while driving during hypoglycemia were similar. Both -/+History groups were equally likely to self-treat with the soft drink (44%/59% respectively, p=.35) while driving during hypoglycemia.

**CONCLUSIONS**

This study demonstrated that type 1 diabetic drivers with a history of recurrent hypoglycemia-related driving mishaps during the previous year differed on several basic levels from drivers with no such history. However, it is important to point out that these groups did not differ in terms of general demographic variables (e.g. age, education BMI), diabetes parameters (e.g. duration of disease, HbA1c, insulin regimens, hypoglycemia unawareness, long-term complications), or driving parameters e.g. driving history, miles driven, Table 1). The exception being that the +History subjects reported three times more episodes of severe hypoglycemia during the previous year. While +History group demonstrated equivalent driving performance during euglycemia, relative to the –History group, their overall driving performance during the 30 minute induction of hypoglycemia from 3.9 to 2.5 mmol/L was worse. Our design does not allow us to determine at what BG level this impairment first manifested itself. In contrast, our –History group did not demonstrate a decay.

Drivers with a positive history of mishaps tended to require more infused dextrose to maintain euglycemia during similar insulin challenges, suggesting these individuals may be more vulnerable to hypoglycemia due to increased glucose utilization. When exposed to progressive mild hypoglycemia, they released less epinephrine, possibly making them more likely to slip into deeper hypoglycemia. Further, when they were experiencing progressive mild hypoglycemia, they demonstrated greater neuroglycopenia as
suggested by a significant worsening of driving performance by 2.5 standard deviations.

Drivers with and without a history of hypoglycemia-related driving mishaps did differ significantly in symptom perception during euglycemia but were symptomatically equivalent during progressive hypoglycemia. Detection of autonomic and neuroglycopenic symptoms is a key way for individuals with type 1 diabetes to recognize hypoglycemia during routine functioning. Not only did +History drivers fail to detect an increase in symptoms during the induction of hypoglycemia, but they actually reported more such symptoms during euglycemia than –History drivers. It is as if the former group has to deal with symptom “noise”, i.e. a background of symptoms occurring during euglycemia that may make it difficult to detect the ‘signal’ of hypoglycemia, in other words a poor symptom to noise ratio. It is not clear from the present study whether this is a general condition for these individuals or if there is something unique to driving that triggers this inversion of symptom perception. Despite these differences in epinephrine release and perceived symptoms, -History (59%) and +History (44%) subjects were similarly likely to self-treat. This may be because self-treatment of hypoglycemia appears to be related to detected difficulties driving and not classic symptoms of hypoglycemia. Further, this relatively low-rate of self-treatment while hypoglycemic is consistent with the subjects’ self-report that they seldom carried fast acting glucose in their car, along with previously reported data indicating drivers are willing to drive with low BG. [10]

Because a recent history of hypoglycemia-related driving mishaps heralds the likelihood of future driving mishaps, [1, 3,13], these findings have several clinical implications: Such high-risk drivers: 1) may require more robust carbohydrate dosing to prevent or to treat hypoglycemia, 2) should be counseled in terms of an appropriate BG threshold when not to begin driving, e.g. 5 mmol/L, which would vary depending on the length of the drive and whether their BG will be rising or falling during the course of the drive, and 3) should be encouraged to immediately stop driving if BG falls <4 mmol/L, treat themselves with sufficient fast acting carbohydrates, and not resume driving until BG is >5 mmol/L. Limitations of this study should be considered. First, like most insulin clamp studies, this data represents a single observation in a laboratory setting. Therefore, the external validity of these findings can not be confirmed. Second, this study was partially based on driving a simulator, not an actual car with real-life traffic and driving demands/risks. Third, this was a relatively small sample of only 38 adult drivers with type 1 diabetes. This small sample size may not have had sufficient power to identify small but potentially important differences between these two groups, such as differences in gender (-History = 34% female as compared to 62% for +History group). Finally, while this cross-over design controlled for affects of antecedent hypoglycemia, an alternative design would have been to separate testing days by two weeks while rigorously avoiding hypoglycemia for two weeks before each testing. However, these limitations are offset by the fact that these a priori findings replicate previous post hoc analyses with an independent sample and different research staff, but employing similar methodologies and technologies. [14] Additionally, the simulator used in this study has been found to predict on-road
driving behaviors [21] and predict future collisions. [22] Given the potential gravity of the consequences of hypoglycemia-related collisions, [9] it would seem clinically prudent to use these findings as a guide when working with individuals who are at a higher risk for hypoglycemia while driving, despite these methodological limitations.

**Author Contributions.** Dr. Daniel J. Cox oversaw the project and was the primary author of this manuscript. In addition to helping prepare the manuscript, Dr. Boris Kovatchev conducted data analysis and Dr. Linda A. Gonder-Frederick coordinated data collection. Dr. Stacey M. Anderson led the inpatient patient management, and Dr. William L. Clarke provided medical oversight for the project.

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**Disclosure.** There are no conflicts of interest for any of the authors related to this manuscript.

**REFERENCES**
10. Clarke WL, Cox DJ, Gonder-Frederick LA, Julian D. To drive or not to drive: That is the decision. JAMA 1999;282(8):750-754
Table 1. Subjects’ descriptive characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>HISTORY</th>
<th>+History</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>22</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>42 ±12.9</td>
<td>42 ±12.8</td>
<td>ns</td>
</tr>
<tr>
<td>% Female (N)</td>
<td>34% (7)</td>
<td>62% (10)</td>
<td>ns</td>
</tr>
<tr>
<td>Education/yrs</td>
<td>15 ±2.6</td>
<td>16 ±2.2</td>
<td>ns</td>
</tr>
<tr>
<td>HbA1c</td>
<td>7.1 ±0.8</td>
<td>7.5 ±0.9</td>
<td>ns</td>
</tr>
<tr>
<td>Yrs. with diabetes</td>
<td>21 ±9.4</td>
<td>21 ±10.8</td>
<td>ns</td>
</tr>
<tr>
<td>Insulin Units/day</td>
<td>42 ±15.5</td>
<td>42 ±32.3</td>
<td>ns</td>
</tr>
<tr>
<td>BMI</td>
<td>27 ±5.2</td>
<td>26 ±4.2</td>
<td>Ns</td>
</tr>
<tr>
<td>% Hypoglycemia Awareness (N)</td>
<td>82% (18)</td>
<td>75% (12)</td>
<td>Ns</td>
</tr>
<tr>
<td>Severe hypoglycemia* in past 12 month</td>
<td>0.5 ±0.7</td>
<td>1.6 ±2.2</td>
<td>&lt;.03</td>
</tr>
<tr>
<td>% Subjective neuropathy</td>
<td>23% (5)</td>
<td>44% (7)</td>
<td>ns</td>
</tr>
<tr>
<td>% Objective Neuropathy (N)</td>
<td>9% (2)</td>
<td>19% (3)</td>
<td>ns</td>
</tr>
<tr>
<td>% Retinopathy (N)</td>
<td>41% (9)</td>
<td>25% (4)</td>
<td>ns</td>
</tr>
<tr>
<td>% Laser eye therapy</td>
<td>4% (1)</td>
<td>12% (2)</td>
<td>Ns</td>
</tr>
<tr>
<td>Years Driving experience</td>
<td>27</td>
<td>27</td>
<td>Ns</td>
</tr>
<tr>
<td>Miles driven/yr</td>
<td>18.5714 +12.040</td>
<td>17.7308 +16.133</td>
<td>Ns</td>
</tr>
<tr>
<td>SMBG before driving</td>
<td>1.3</td>
<td>1.7</td>
<td>Ns</td>
</tr>
<tr>
<td>Fast acting sugar in car</td>
<td>2.0</td>
<td>3.0</td>
<td>Ns</td>
</tr>
<tr>
<td># Mild hypo while driving in past 6 months</td>
<td>0.7</td>
<td>1.1</td>
<td>Ns</td>
</tr>
<tr>
<td># Driving mishaps in past 12 months</td>
<td>0</td>
<td>2.8</td>
<td>.0001</td>
</tr>
<tr>
<td>Hypoglycemic nadir, mmol/L</td>
<td>2.7±0.9</td>
<td>2.6±0.3</td>
<td></td>
</tr>
<tr>
<td>Peak epinephrine during hypoglycemia</td>
<td>345 ±178</td>
<td>217 ±137</td>
<td>=.05</td>
</tr>
<tr>
<td>% Self-Treatment during hypoglycemic drive</td>
<td>59% (13)</td>
<td>44% (7)</td>
<td>Ns</td>
</tr>
</tbody>
</table>

1 Hypoglycemia awareness was defined using the criteria reported by Clarke et al [25]
2 DCCT criteria for severe hypoglycemia was employed, i.e. episodes where individual was unable to treat him/herself, either because s/he was stuporous, unconscious or had a seizure.
3 Mean rating on a scale where 1= Always, 2= Frequently, 3= Seldom, 4= Never
Figure 1. Randomized, cross-over design controlling for practice and antecedent hypoglycemia effects influencing Condition effects.

Figure 2. Impaired Driving Score during Eu- and Hypoglycemic conditions for +/-History subjects

Black bar = +History
Striped bar = -History

Figure 3. Mean number of significant Autonomic and Neuroglycopenic symptoms endorsed while driving under eu- and hypoglycemic conditions for +/-History subjects, with p levels reflecting differences between groups at euglycemia.

Black bar = +History
Striped bar = -History

Figure 1

<table>
<thead>
<tr>
<th>Recruit drivers with type 1 diabetes who: had no recent driving mishaps (-Hx, N=22) or recent multiple driving mishaps (+Hx, N=16)</th>
</tr>
</thead>
</table>
| Half of each patient group randomized to each sequence

<table>
<thead>
<tr>
<th>Euglycemia</th>
<th>Progressive Hypo.</th>
<th>Day 1</th>
<th>Video</th>
<th>Drive</th>
<th>Day 1</th>
<th>Video</th>
<th>Drive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 2</td>
<td>Drive</td>
<td>Video</td>
<td>Drive</td>
<td>Video</td>
<td>Day 2</td>
<td>Drive</td>
<td>Video</td>
</tr>
</tbody>
</table>
Figure 2

IDS

+History
-History

Euglycemia Hypoglycemia

Figure 3

Autonomic Symptoms

Neuroglycopenic Symptoms

p < .001

p < .018