Hyperglycemia and Externalizing Behavior in Children With Type 1 Diabetes

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OBJECTIVE — Ancedotally, parents report behavioral changes in their diabetic children who have fluctuating blood glucose levels. This study aimed to test associations between intercurrent glycemia and child behavior in an ambulant setting.

RESEARCH DESIGN AND METHODS — Prepubertal children attending the Royal Children's Hospital, Melbourne, Australia, with type 1 diabetes received glycemic assessment and simultaneous behavioral assessment on two occasions 6 months apart. Subjects wore a continuous glucose monitor over a 72-h period, and parents completed the Behavior Assessment System for Children at the two study time points.

RESULTS — There was a high correlation between intra-individual externalizing and internalizing behavior scores ($r = 0.88$, $P < 0.001$ and $r = 0.81$, $P < 0.001$, respectively) at the two time points. Mean blood glucose (MBG) was significantly associated with the mean externalizing behavior score ($\beta = 1.7$ [95% CI 0.6–2.8], adjusted $r^2 = 0.088$). Percentage of time in the normal ($r = -0.2$ [−0.3 to −0.5], adjusted $r^2 = 0.068$) and high ($r = 0.2$ [0.07–0.3], adjusted $r^2 = 0.089$) glycemic ranges were significantly associated with the mean externalizing behavior score. For every 5% increase in time in the normal glycemic range, there was a decrease in the externalizing behavior score of 1.0, and for every 5% increase in time in the high glycemic range there was an increase in the externalizing behavior score of 1.0. There was no significant association between MBG and the mean internalizing behavior score.

CONCLUSIONS — Externalizing behaviors were associated with intercurrent glycemic status. These findings underscore the importance of understanding the mechanisms of this association and how it might impact ultimate diabetes outcomes.

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Parents of children with type 1 diabetes often report that they can detect elevations in their child's blood glucose due to changes in outward behavioral patterns. These reports, however, are entirely anecdotal, and to date, there has been little direct inquiry in this phenomenon. In particular, both the existence and causality of the association have yet to be confirmed. Much of the literature that exists on the impact of behavior on diabetes or vice versa relates to long-term effects on poor metabolic control (1–4) or to transient changes during acute severe episodes of hypoglycemia (5,6). Recently, studies have identified impairment of cognitive performance and mood in adults with either type 1 or type 2 diabetes (7,8). Poor metabolic control has also been associated with disengagement and negativity in adolescents with type 1 diabetes (9). High levels of externalizing behaviors (e.g., aggression, overactivity, conduct problems) at diagnosis are strongly predictive of externalizing behaviors in adolescence (10), and these behaviors, in turn, are predictive of poor metabolic control and mental health problems in middle-aged adults (11).

The purpose of this study was to test for any possible association between childhood behavior and intercurrent glycemia. To address direct parental observations of behavior, we elected to conduct this study in a noncontrolled ambulant context using continuous glucose monitoring techniques and standardized parent-report behavioral questionnaires.

RESEARCH DESIGN AND METHODS

— This study was conducted prospectively in 2003 and 2004 over a 6-month period and was approved by the Human Ethics Research Committee at the Royal Children's Hospital (RCH), Melbourne, Australia.

Primary school–aged children attending the diabetes outpatient clinic of RCH with >2 years duration of type 1 diabetes aged 5–10 years on 1 February 2003 were invited to join this study. The RCH clinic cares for ~1,350 children and adolescents with type 1 diabetes. This group is demographically representative of the community in Melbourne, Australia. Children were recruited sequentially over a 3-month period during their routine attendance at the outpatient clinic and received continuous glycemic and simultaneous behavioral assessment on two occasions 6 months apart.

Continuous glycemic assessment

Each child wore a continuous glucose monitor (Minimed, Northridge, CA) (12) over a 72-h period at the two study time points. This procedure has been previously described elsewhere (12). After each 72-h recording period, data were downloaded (using CGMS Gold software) and cleaned to remove invalid data. Invalid data were defined as occasions where there were less than four calibrations from finger-prick blood glucose readings in a 24-h period or a calibration was not carried out within an 8-h period. Data were summarized using an algorithm previously reported by this group (13). Mean blood glucose (MBG) was cal-

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Abbreviations: BASC, Behavior Assessment System for Children; CGMS, continuous glucose monitor system; MBG, mean blood glucose; RCH, Royal Children's Hospital.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

culated as was percentage of time spent in low (continuous glucose monitoring system [CGMS] <4 mmol/l), normal (4–12 mmol/l), and high (>12 mmol/l) glucose ranges.

Behavioral measures

On both occasions when CGMS was applied, parents were asked to complete the Behavior Assessment System for Children (BASC) (14). This is a standardized, validated, parent-report instrument that takes ~20 min to complete on each occasion and reflects the child's typical behavior over the previous 6 months. To minimize the risk that parental ratings are influenced by factors extraneous to the child's actual behavior, parents are asked to report on the occurrence and frequency of specific behaviors and not on their perceptions and feelings regarding the child's behavior (e.g., "Does your child hit other children almost always? Often? Sometimes? Never?" rather than "Is your child aggressive?"). Analyses of BASC data were carried out using BASC Enhanced ASSIST (version 2.0), which generates summary *T*-scores (mean of 50 and SD of 10) standardized for age and sex for externalizing and internalizing behavior. Externalizing behavior comprises hyperactivity, aggression, and conduct scores, whereas internalizing behavior comprises anxiety, depression, and somatization scores. High scores indicate greater psychopathology.

Statistical analysis

The degree of agreement between intra-individual measurements on the two occasions was evaluated using the correlation coefficient (*r*). Linear regression was used to evaluate the relationship between behavior scores and glycemic measurements.

RESULTS — A total of 42 children (27 female and 15 male) aged 5–10 years consented to be in the study. At the time of recruitment, this cohort was representative of the total RCH clinic population aged 5–10 years (mean age 8.0 vs. 7.6 years for the study cohort vs. the overal 5- to 10-year-old clinic cohort, respectively, $P = 0.25$) and A1C levels (8.2 vs. 8.1%, $P = 0.60$). All patients completed the assessment according to the protocol. Preliminary analyses showed that the relationship between dependent and independent variables at the two observational time points was similar such that data from both time points were pooled providing 84 glycemic and behavioral paired datasets.

Table 1—*Characteristics of the study cohort at baseline and 6 months*

	Baseline	6 months
n	42	42
Age (years)	8.3 ± 1.4	8.9 ± 1.4
Sex (male/female)	15/27	15/27
Total daily insulin dose (units · kg^{-1} · day^{-1})	0.87 ± 0.2	0.9 ± 0.2
A1C (%)	8.6 ± 0.8	8.5 ± 0.8
Glycemic measures		
MBG (mmol/l)	10.8 ± 1.8	11.6 ± 2.1
Percentage of time in low glycemic range	7.4 ± 8.6	6.9 ± 7.9
Percentage of time in normal glycemic range	53.7 ± 14.0	47.1 ± 15.6
Percentage of time in high glycemic range	38.9 ± 14.9	46.0 ± 17.8
Behavioral variables		
Externalizing behavior score	48.6 ± 9.3	48.1 ± 11.3
Internalizing behavior score	54.2 ± 12.2	52.9 ± 14.0

Data are means ± SD.

Sample characteristics are shown in Table 1. Forty patients were receiving insulin in a twice-daily mixing regime, two patients were receiving insulin in a 3–4 injection regime, and zero patients were receiving insulin pump therapy. The mean number of valid hours per CGMS trace was 73.9 h. Glycemic and behavioral data were normally distributed.

Glycemic data

MBG. The overall MBG value was 11.2 ± 2 mmol/l (mean ± SD). The intra-individual correlation of MBG values between the two time points studied (0 and 6 months) was not significant ($r = 0.04$, $P = 0.83$). In individual patients, MBG was moderately correlated with intercurrent A1C ($r = 0.43$ [95% CI 0.24–0.59], $P < 0.001$).

Percentage of time in various glycemic ranges. The overall mean percentage of time spent in the low (<4 mmol/l), normal (4–12 mmol/l), and high (>12 mmol/l) CGMS ranges were 7.1 ± 8.2, 50.4 ± 15.1, and 42.4 ± 16.7%, respectively, and there were poor correlations of the intra-individual measures at the two time points (low, $r = 0.14$, $P = 0.36$; normal, $r = 0.33$, $P = 0.03$; and high, $r = 0.10$, $P = 0.53$).

Behavioral data

Externalizing behavior scores. There was a high correlation between intra-individual externalizing behavior scores at the time points studied ($r = 0.88$, $P < 0.001$) (Fig. 1*A*). In view of this, data from the two time points were pooled to calculate an overall mean externalizing behavior *T*-score (48.3 ± 10.3).

Internalizing behavior scores. There was high correlation between intra-individual internalizing behavior scores across the two time points studied ($r = 0.81$, $P < 0.001$) (Fig. 1*B*). Using pooled data from both time points, the overall mean internalizing behavioral *T*-score was 53.5 ± 13.1.

Associations between glycemic measures and behavior scores

MBG and behavior scores. MBG was significantly associated with the mean externalizing behavior score (regression coefficient = 1.7 [95% CI 0.6–2.8], adjusted $r^2 = 0.088$) (Fig. 2*A*). This indicates that on average, for every 1 mmol/l rise in MBG, there was a concomitant rise of 1.7 in the externalizing behavior score, and variation in the MBG explained 8.8% of the variance in the group mean externalizing behavior score. There was no significant association between MBG and the mean internalizing behavior score.

Percentage of time in various glycemic ranges and behavior scores. Percentage of time in the normal ($r = -0.2$ [95% CI −0.3 to −0.5], adjusted $r^2 = 0.068$) and high ($r = 0.2$ [0.07–0.3], adjusted $r^2 = 0.089$) glycemic ranges were significantly associated with the mean externalizing behavior score (Fig. 2*B* and *C*). These data indicated that for every 5% increase in time in the normal glycemic range, there was a decrease in the externalizing behavior score of 1.0 and that for every 5% increase in time in the high glycemic range, there was an increase in the externalizing behavior score of 1.0. Variation in either percentage of time in the normal or high glycemic ranges explained 6.8 and 8.9% of the variance in the overall mean externalizing behavior score, respectively. There were no significant associations between percentage of time in the low gly-

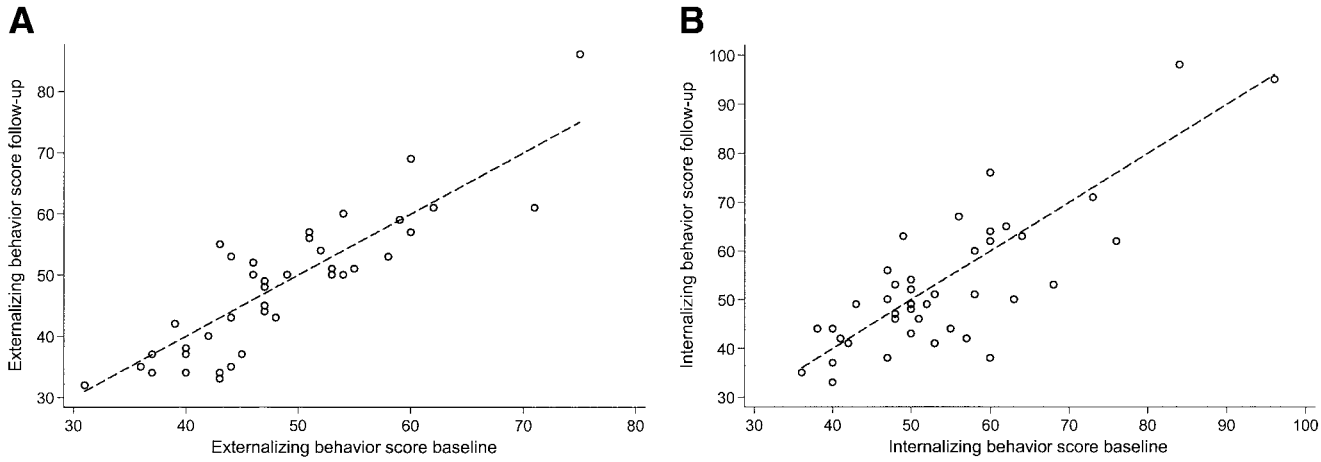

Figure 1—*Intra-individual association of behavioral measures at baseline and 6 months.* A*: Externalizing behavior scores.* B*: Internalizing behavior scores.*

cemic range and externalizing behavior scores, and significant associations were not found between internalizing behavior scores and the percentage of times in the normal, high, or low glycemic ranges.

CONCLUSIONS — In this study of a primary school–aged cohort of children with type 1 diabetes, we found that higher MBG values, increased percentage of time in the high glycemic range, and decreased percentage of time in the normal glycemic range were all associated with higher externalizing behavior scores. Our findings are noteworthy in that we have demonstrated consistency in the relationship between the three glycemic measures and externalizing behavior, with higher MBG and percentage of time in high glycemic ranges being associated with more behavioral problems and higher percentage of time in the normal glycemic range being associated with fewer problems. Overall, MBG and percentage of time in high and

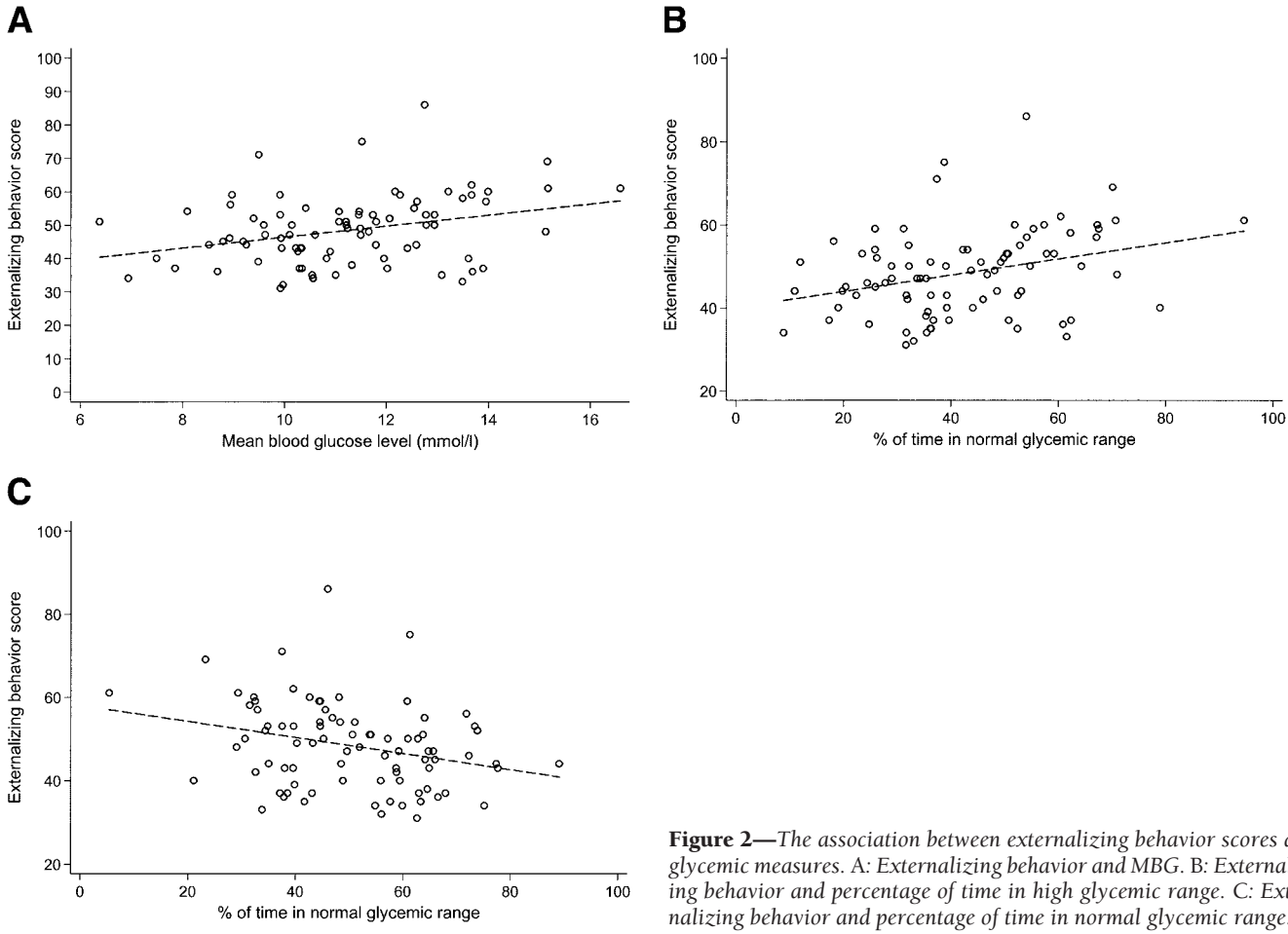

Figure 2—*The association between externalizing behavior scores and glycemic measures.* A*: Externalizing behavior and MBG.* B*: Externalizing behavior and percentage of time in high glycemic range.* C*: Externalizing behavior and percentage of time in normal glycemic range.*

normal glycemic ranges explained between 7 and 9% of the variance in externalizing behaviors. Multiple independent and interacting factors are likely to influence behavior; hence, identifying a single factor that explains this amount of the variance in behavioral status is clinically meaningful (15).

Although this study examined short-term glycemic control using only a CGMS trace, previous studies have illustrated that MBG levels from the trace correlate strongly with A1C (16,17). A positive correlation between MBG and A1C was also seen in this study, indicating that a short-term CGMS trace is representative of long-term metabolic control. This is also consistent with previously reported associations between high A1C levels and high externalizing behaviorial scores (10, 11).

Externalizing behaviors identified on the BASC include hyperactivity, aggression, and conduct disorders. These behaviors are similar to those identified anecdotally by parents as being associated with higher blood glucose levels. In this study, we were unable to determine causality in the association between the behavioral variables and glycemia. However, the tight intra-individual correlation between externalizing behavior scores at both time points and lack of correlation between intra-individual MBG at both time points suggest that externalizing behaviorial problems may provide the background context in which hyperglycemia occurs. This hypothesis requires testing in future studies, but the interpretation is supported by other research that shows that externalizing behavior scores at the time of diagnosis were significant determinants of poor metabolic outcomes up to 10–15 years later (10,11).

There is evidence in previous literature of an association between internalizing symptoms and better regimen adherence/metabolic control (4,18–20), suggesting that neurotic symptoms may either contribute to or result from obsessive preoccupation with the demands of strict adherence to treatment regimens. Despite internalizing behavior scores showing the same intra-individual consistency as externalizing behavior scores across the two time points, we were unable to show any significant association between these and glycemic measures. It is not clear why this association was not apparent in the current study, but it is possible that internalizing symptoms emerge over a longer period, making it difficult to identify associations in the 6-month time frame used in this study. Interestingly, there was no correlation found between any of the behavioral variables and percentage of time spent in the low glucose range or glycemic variation. Diaries linked to the CGMS traces showed high levels of "hypoglycemic unawareness" (data not shown). Therefore, it is possible that when children lack a sympathetic counter-regulatory response to hypoglycemia and are "unaware" of events, hypoglycemia does not arouse anxiety and has no lasting impact on either internalizing or externalizing behavior. These hypotheses remain to be tested.

This is the first report of a study examining behavior and intercurrent glycemia using CGMS in an ambulant noncontrolled setting. Our findings provide some support for parental observation of an association between externalizing behaviorial problems and intercurrent hyperglycemia. As such, our findings are consistent with the previously recognized association between behaviorial problems and longer-term metabolic control, as reflected in A1C levels. The current findings are also consistent with the developmental psychopathology literature that shows moderate to high stability in externalizing behaviors, particularly in the absence of treatment (21). Whereas causality between externalizing behavior and hyperglycemia remains an open question, these findings underscore the importance of understanding the mechanisms of this association and how it might impact on ultimate diabetes outcomes. Externalizing behaviorial problems are easily identifiable and effective treatments available, particularly if implemented early (22). An effective and timely intervention with young children presenting with externalizing behaviorial problems may have a dual benefit in reducing morbidity in both mental and physical health outcomes.

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