Association Between HbA1c Variability and Risk of Microvascular Complications in Adolescents with Type 1 Diabetes

Sohaib A Virk1,2, Kim C Donaghue, PhD FRACP1,3, Yoon Hi Cho FRACP 1, Paul Benitez-Aguirre, PhD FRACP1, Stephen Hing FRACOS1, Alison Pryke1, Albert Chan MAppStat1, Maria E Craig, PhD, FRACP1,2,3

Institute of Endocrinology and Diabetes, The Children’s Hospital at Westmead, Sydney, New S Wales, Australia1; School of Women’s and Children’s Health, University of New S Wales, Sydney, New S Wales, Australia2; Discipline of Pediatrics and Child Health, University of Sydney, Sydney, New S Wales, Australia3

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Context: There is a paucity of data regarding the association between glycosylated hemoglobin variability (HbA1c) and risk of microvascular complications in adolescents with type 1 diabetes (T1D).

Objective: To investigate the association between HbA1c variability and risk of microvascular complications in adolescents with T1D.

Design: Prospective cohort study from 1990–2014 (median follow-up 8.1 years).

Setting: Tertiary pediatric hospital.

Participants: 1706 adolescents (aged 12–20 minimum diabetes duration 5 years) with median age of 15.9 years [interquartile range 14.3–17.5] and diabetes duration of 8.1 years [6.3–10.8].

Main Outcome Measures: Glycemic variability was computed as the standard deviation of all HbA1c measurements (SD-HbA1c) after diagnosis. Retinopathy was detected using seven-field fundal photography, renal function assessed using albumin excretion rate (AER), peripheral neuropathy detected using thermal and vibration threshold testing, and cardiac autonomic neuropathy detected using time- and frequency-domain analyses of electrocardiogram recordings. Generalized estimating equations were used to examine the relationship between complications outcomes and HbA1c variability, after adjusting for known risk factors including HbA1c, diabetes duration, blood pressure and lipids.

Results: In multivariable analysis, SD-HbA1c was associated with early retinopathy (odds ratio [OR] 1.32; 95% CI, 1.00–1.73), albuminuria (OR 1.81; 1.04–3.14), increased log10AER (OR 1.10; 1.05–1.15) and cardiac autonomic neuropathy (OR 2.28; 1.23–4.21), but not peripheral neuropathy.

Conclusions: Greater HbA1c variability predicts retinopathy, early nephropathy and cardiac autonomic neuropathy, in addition to established risk factors, in adolescents with type 1 diabetes. Minimizing long term fluctuations in glycemia may provide additional protection against the development of microvascular complications.
The Diabetes Control and Complications Trial (DCCT) conclusively demonstrated the risk of microvascular complications rises markedly as glycated hemoglobin (HbA1c) increases (1). However, even within the same mean HbA1c levels, individuals can vary widely in their glycemic excursions, and more recent studies suggest visit-to-visit variation in HbA1c may be an additional risk factor for the development of retinopathy (2–4) and nephropathy (4, 5) in adults.

To date, however, there have been no studies assessing the association between HbA1c fluctuations and the risk of either peripheral or autonomic neuropathy. There is also a paucity of evidence on the relationship between HbA1c variability and complications risk in children and adolescents with type 1 diabetes (5). The clinical significance of HbA1c variability is of particular interest in this group given their distinct risk factors for complications (eg, puberty) and the unique psychosocial and physiological challenges associated with the management of their glycemia (6).

The objective of this study was thus to examine the association between HbA1c variability and the development of microvascular complications in a longitudinal cohort of young people with type 1 diabetes.

**Research Design and Methods**

**Study Population**

The study population consisted of adolescents with type 1 diabetes who were prospectively assessed for complications at The Children’s Hospital at Westmead from January 1990 to May 2014. Inclusion criteria were age between 12 and 20 years, diabetes duration of at least five years, and availability of more than five serial HbA1c measurements since diagnosis. This latter criterion was instituted as a larger number of HbA1c levels, individuals can vary widely in their glycemic excursions, and more recent studies suggest visit-to-visit variation in HbA1c may be an additional risk factor for the development of retinopathy (2–4) and nephropathy (4, 5) in adults.

**Assessment of Glycemic Variability**

Glycemic control was assessed by measuring glycated hemoglobin (GHb) calorimetrically before February 1994 (8) and afterward by measurement of HbA1c using high performance liquid chromatography (Diamat Bio-Rad analyzer, Bio-Rad, Hercules, CA; nondiabetic range 4%–6%). GHb values were retained from all patients (and their families if aged < 18 years).

Glycemic control was assessed by measuring glycated hemoglobin (GHb) calorimetrically before February 1994 (8) and afterward by measurement of HbA1c using high performance liquid chromatography (Diamat Bio-Rad analyzer, Bio-Rad, Hercules, CA; nondiabetic range 4%–6%). GHb values were converted to HbA1c (Diamat = 1.9088 + 0.0043 x GHb; r = 0.92) (9).

For each patient, the intrapersonal mean and standard deviation (SD) of all recorded glycemic control measurements were calculated, and the SD-HbA1c was considered a measure of glycemic variability. As the number of individual visits (n) could influence the SD-HbA1c (with fewer visits likely to artificially inflate SD), values for SD-HbA1c were divided by \( \sqrt{\frac{n-1}{n}} \) to adjust for this possibility (4). We also calculated coefficient of variation (CV), a normalized measure of glycemic variability. CV was computed as the division of SD-HbA1c by a factor of mean HbA1c (ie, \( CV = \frac{SD-HbA1c}{MeanHbA1c/10} \)).

**Complications Assessment**

Retinopathy was assessed by seven-field stereoscopic fundal photography using the IMAGEnet2000Lite system to digitalize images. The same ophthalmologist graded photographs according to the modified Airlie House classification (10). Retinopathy was defined as the presence of at least one microaneurysm or hemorrhage (grade 21/10 or higher) in either eye.

Albumin excretion rate (AER) was determined using the mean of three consecutive timed overnight urine collections. Albumin was measured using Pharmacia Radioimmunoassay (Beckham Coulter Australia) before 2000, Immage Immunoassay (Beckham Coulter Australia) from 2000 to 2003, and Immulite Immunoassay (Simens Healthcare) thereafter. Regression equations for albumin had high correlation (\( R^2 = 0.98; y\)-intercept of −0.5 and −0.56 mg/L). Albuminuria was defined as mean AER µ/kg or mean ACR 2.8 mg/mmol (male) and 4.1 (female) (12).

Peripheral nerve function was assessed by thermal threshold testing for hot and cold sensation at the dorsum of the left foot and vibration threshold testing at the left malleolus and left great toe (Neurosensory TSA-II and Vibratory Sensory Analyzer, Medoc Ltd, Ramat Yishai, Israel), as previously described (11). Cardiac autonomic neuropathy (CAN) was assessed by measures of heart rate variability (HRV) obtained from analysis of 10-minute continuous electrocardiogram (ECG) recordings using the LabChart Pro (ADInstruments, Sydney, Australia). Derived time-domain measures included the standard deviation of mean NN intervals (where NN is the time between adjacent QRS complexes) and the root mean squared differences of successive NN intervals. Frequency-domain measures included low-frequency (LF) and high-frequency (HF) spectral components, and the LF: HF ratio. Together, these measures provide an estimate of both overall HRV and the relative parasympathetic and sympathetic balance (12). Age- and gender-adjusted reference ranges used to define abnormality were derived from nondiabetic adolescent controls (9). Peripheral neuropathy was defined as either a vibration or thermal threshold test score above the 95th percentile. Cardiac autonomic neuropathy was defined as a measurement below the fifth percentile on at least one time-domain or frequency-domain measure of HRV.

Height, weight and BMI from each complications assessment were converted to z scores using the 2000 Centers for Disease Control (CDC) reference standards (13). Systolic and diastolic blood pressure (BP) (SBP and DBP) z scores for age and sex were derived using the U.S. Task Force Report (14). Cholesterol was measured using a Beckman CX5 from 1990–1999, a Dimension RXL from 2000–2005 and a Vitros analyzer (Ortho Clinical Diagnostics) thereafter. Participants were classified into either a socioeconomically disadvantaged (deciles 1–3) or socioeconomically advantaged (deciles 4–10) group using a postcode-based system derived from the Australian Bureau of Statistics Socio–Economic Indexes for Areas (SEIFA) database (15).
Statistical Analysis

Descriptive statistics are reported using means SD for normally distributed continuous variables, and median (interquartile range) for skewed data. Differences between two groups were analyzed using Independent Samples t test for normally distributed variables and the Mann-Whitney U test for skewed data. Trends across more than two groups were analyzed using linear polynomial contrasts (ANOVA) for normally distributed variables and the Jonckheere-Terpstra test for skewed data. Categorical variables were compared using Pearson’s χ² or linear-by-linear association test (trend across more than two groups). Multiple linear regression was used to identify baseline factors by-linear association test (trend across more than two groups).

To longitudinally examine the association between glycemic variability and microvascular complications, generalized estimating equations were used so that correlations between repeat visits for an individual patient could be taken into account (16). Regression models were adjusted for the following covariates: mean Hba1c (%), age (years), sex, diabetes duration (years), SBP and DBP (z scores), cholesterol (mmol/L), height (z score), BMI (z score) and socioeconomic disadvantage. Spearman’s rank correlation coefficient (r_s) was used to assess strength of association between covariates and screen for collinearity.

To account for the possible influence of mean Hba1c on SD-Hba1c, two models were constructed. Model 1 used SD-Hba1c as a measure of glycemic variability while Model 2 used Hba1c. Clinically relevant interaction terms (eg, age*SD-Hba1c, age*CV, sex*SD-Hba1c, sex*CV, duration*SD-Hba1c, duration*CV, age*sex*SD-Hba1c, age*sex*CV, duration*sex*SD-Hba1c, duration*sex*CV) were not significant, and were excluded from the final models. Quadratic terms for SD-Hba1c and CV used to test for curvature were not significant. The Quasi Likelihood Under Independence Model Criterion (QIC) was used to summarize goodness of fit of multivariable models (Table 3). There was no association between peripheral neuropathy and glycemic variability (as measured by either SD-Hba1c or CV).

Results

Overall, 1,706 patients (47% male) met the inclusion criteria and results from 3,995 complications assessments were included in the analysis. Those excluded due to the lack of serial Hba1c measurements (n = 301) had significantly shorter diabetes duration (median 7.1 vs. 8.1 year; P < .001) but were not significantly different in regards to proportion male, socioeconomic disadvantage, insulin dose, BP, cholesterol, or BMI SDS.

Median age at last assessment was 15.9 years [14.3–17.5], diabetes duration 8.1 year [6.3–10.8] and Hba1c measurements per patient 22 [14–29], ie, 2.7 per patient per year. At last assessment, median intra-personal mean Hba1c was 8.5% [7.9–9.0] (69 mmol/mol [63–75]) and SD-Hba1c was 0.95% [0.71–1.26]. There was a significant correlation between the last single-measurement of Hba1c and the mean of serial Hba1c (r_s 0.570; P < .001).

Patient characteristics and complication rates at last assessment are presented in Table 1, stratified by ascending quartiles of SD-Hba1c. Those with higher SD-Hba1c were older, had longer diabetes duration, shorter stature, higher daily insulin dose, mean Hba1c, BP (z scores) and cholesterol, and were less likely to be treated with intensive insulin therapy.

The prevalence of retinopathy, albuminuria and cardiac autonomic neuropathy (CAN) increased significantly across ascending quartiles of SD-Hba1c (Table 1, Figure 1). Patients in higher quartiles of SD-Hba1c displayed significantly higher median AER. However, no trend was observed for peripheral neuropathy.

Table 2 shows the relationship between glycemic variability and microvascular complications after adjusting for mean Hba1c and other covariates, using generalized estimating equations. Model 1 included SD-Hba1c while Model 2 included Hba1c. CV. Using either measure, greater glycemic variability was associated with the development of retinopathy, albuminuria, increased log10AER and CAN after adjustment for known risk factors. A one-unit increase in SD-Hba1c was associated with 32% higher odds of retinopathy, 81% higher odds of albuminuria, 128% higher odds of CAN and 10% increase in log10AER. For each of these outcomes, the addition of either SD-Hba1c or CV improved the goodness of fit of the multivariable models (Table 3). There was no association between peripheral neuropathy and glycemic variability (as measured by either SD-Hba1c or CV).

Conclusions

In this observational study involving 1,706 adolescents with type 1 diabetes, Hba1c variability was significantly associated with an increased risk of retinopathy, albuminuria, elevated albumin excretion rate and CAN after adjusting for established risk factors. This is the first time that glycemic variability has been associated with CAN. While our results for retinopathy and early nephropathy are consistent with a recent analysis of the DCCT (4) as well as several cohort studies involving adults with type 1 diabetes (2, 3, 17), we demonstrate the association between Hba1c instability and these complications in an adolescent population, in whom such clinical data had been scarce (5). Moreover, in contrast to the more advanced endpoints employed in previous studies, we defined retinopathy as a one-level worsening on the Early Treatment Diabetic Retinopathy Scale and examined early elevation of AER, which predicts future development of microalbu-
minuria (18). Thus, by employing earlier clinical end-
points, we have demonstrated the association with HbA1c
variability applies across the entire spectrum of retinal and
renal disease.

Our most novel finding was the significant association
between glycemic variability and CAN. A one-unit in-
crease in SD-HbA1c more than doubled the odds of CAN.
The effect size was greater than that observed for any other
microvascular complication, and is of substantial clinical
significance considering that CAN is linked with increased
mortality and a higher risk of sudden cardiac death (19).
Furthermore, in the case of CAN, the impact of glycemic
variability was considerably greater than that of mean
HbA1c, which had a comparatively modest effect (Table
2). This raises the question of whether fluctuations in gly-
cemia may play a greater role in the development of CAN
than hyperglycemia itself.

In contrast, peripheral neuropathy was not associated
with HbA1c variability. The conflicting results for auto-
nomic and peripheral neuropathy are particularly surpris-
ing given the strong epidemiological data supporting their
shared association with hyperglycemia and other meta-
bolic risk factors (20, 21). The negative finding for pe-
ripheral neuropathy is almost certainly not a chance result
considering both the point estimate of the odds ratio (OR)
and the value of the significance test approach unity.
Moreover, given the large sample size and relatively high
event rate, the analysis was sufficiently powered to detect
even a weak association. These results may instead reflect
differences in the sensitivity of autonomic and peripheral
nerves or the effect of unknown confounders that were not
adjusted for in the present study.

There are several possible explanations for the associ-
ation observed between glycemic variability and increased
complications risk. There may be underlying confounders
driving this relationship, such as the effect of residual β-cell function and endogenous insulin secretion, which is plausible considering glycemic variability may directly contribute to β-cell apoptosis (23). Alternatively, comorbidities and factors affecting treatment compliance may have con-
tributed to both higher glycemic variability and an increased risk of microvascular complications in this cohort.

It has been hypothesized that fluctu-
ations in HbA1c independently
contribute to increased oxidative
stress, which plays a key role in the
pathogenesis of diabetic complica-
tions (4, 22). This relationship be-
tween HbA1c variability and oxidative stress is extrapo-
lated from animal and in vitro studies that show increased
superoxide production in the setting of higher short-term
(within-day) glucose variability (23–25). However, in
studies of individuals with type 1 diabetes, short-term glu-
cose variability is not associated with oxidative stress (26)
or the risk of microvascular complications (27–30). Other
putative mechanisms include the induction of inflamma-
tory cytokines (33) or stimulation of epigenetic changes
that may promote systemic inflammation (34).

Another possible underlying mechanism may be the
“normoglycemic re-entry phenomenon.” whereby reti-
nopathy frequently worsens following a reduction in
HbA1c before improving as glycemic control is main-
tained (31). However, patients with widely fluctuating
HbA1c may be caught in a cycle where the transient wors-
ening associated with periods of low glycemia is followed
by hyperglycemia-induced damage, and vice versa. Al-
though this phenomenon has been mainly observed for
retinopathy, homeostatic disturbances caused by an un-
stable glycemic environment may also be detrimental for
other complications (17). Alternatively, the association
with HbA1c variability may be related to the “metabolic
memory” hypothesis, which proposes that periods of hy-
perglycemia are “remembered” in the organs in which
microvascular disease later occurs. This is supported by
data from the Epidemiology of Diabetes Intervention and
Complications (EDIC) study demonstrating early glyce-
mic control is a key determinant of future complications
risk (32–35). Moreover, the metabolic memory effect is
weakest for peripheral neuropathy, which may partially
explain its lack of an association with glycemic variability
in the present study (36).

Our findings have several implications for clinical prac-
Table 1. Characteristics and complication rates in adolescents with type 1 diabetes stratified by ascending quartiles of glycemic variability (HbA1c SD)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
<th>4th</th>
<th>P-value for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>426</td>
<td>427</td>
<td>427</td>
<td>426</td>
<td>-</td>
</tr>
<tr>
<td>Male</td>
<td>196 (46)</td>
<td>208 (49)</td>
<td>214 (50)</td>
<td>186 (44)</td>
<td>0.603</td>
</tr>
<tr>
<td>Age (years)</td>
<td>15.4 [13.9 – 17.2]</td>
<td>15.9 [14.3 – 17.3]</td>
<td>16.0 [14.3 – 17.5]</td>
<td>16.3 [15.0 – 17.7]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes duration (years)</td>
<td>7.6 [6.2 – 10.0]</td>
<td>8.0 [6.4 – 10.6]</td>
<td>8.4 [6.6 – 11.1]</td>
<td>8.3 [6.3 – 11.1]</td>
<td>0.006</td>
</tr>
<tr>
<td>Mean HbA1c (%)</td>
<td>8.0 [7.5 – 8.4]</td>
<td>8.3 [7.9 – 8.8]</td>
<td>8.6 [8.1 – 9.1]</td>
<td>9.0 [8.5 – 9.7]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean HbA1c (mmol/mol)</td>
<td>64 [58 – 68]</td>
<td>67 [63 – 73]</td>
<td>70 [65 – 76]</td>
<td>75 [69 – 83]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Insulin dose (units/kg/day)</td>
<td>1.01 [0.88 – 1.25]</td>
<td>1.09 [0.88 – 1.27]</td>
<td>1.13 [0.92 – 1.39]</td>
<td>1.11 [0.91 – 1.34]</td>
<td>-0.001</td>
</tr>
<tr>
<td>Height SDS</td>
<td>0.29 ± 1.00</td>
<td>0.16 ± 1.02</td>
<td>0.17 ± 1.01</td>
<td>0.00 ± 0.97</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight SDS</td>
<td>0.76 [0.18 – 1.35]</td>
<td>0.77 [0.12 – 1.27]</td>
<td>0.79 [0.18 – 1.35]</td>
<td>0.69 [0.05 – 1.14]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI SDS</td>
<td>0.68 [0.13 – 1.24]</td>
<td>0.75 [0.23 – 1.21]</td>
<td>0.79 [0.22 – 1.31]</td>
<td>0.65 [0.13 – 1.14]</td>
<td>0.499</td>
</tr>
<tr>
<td>Cholesterol (mmol/liter)</td>
<td>4.3 [3.8 – 4.8]</td>
<td>4.4 [3.9 – 5.0]</td>
<td>4.3 [3.8 – 5.0]</td>
<td>4.6 [4.0 – 5.2]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP SDS</td>
<td>-0.16 [-0.83 – 0.61]</td>
<td>0.02 [-0.70 – -0.63]</td>
<td>0.15 [-0.59 – -0.63]</td>
<td>0.17 [-0.37 – -0.92]</td>
<td>-0.001</td>
</tr>
<tr>
<td>DBP SDS</td>
<td>0.19 [-0.23 – 0.81]</td>
<td>0.34 [-0.20 – 0.92]</td>
<td>0.56 [-0.05 – -0.92]</td>
<td>0.74 [0.19 – -1.00]</td>
<td>-0.001</td>
</tr>
<tr>
<td>3 injections or CSII</td>
<td>55/424 (13)</td>
<td>70/426 (16)</td>
<td>62/419 (15)</td>
<td>59/421 (14)</td>
<td>0.845</td>
</tr>
<tr>
<td>3 Complications</td>
<td>357/424 (84)</td>
<td>345/420 (82)</td>
<td>264/421 (63)</td>
<td>213/421 (51)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Complications:
- Retinopathy: 64/414 (16) vs. 102/414 (25), 123/408 (30), 152/405 (38), <0.001
- Albuminuria: 13/378 (3) vs. 7/364 (2), 14/353 (4), 27/304 (9), <0.001
- Median AER: 4.73 [3.42 – 5.73] vs. 4.84 [3.63 – 5.73] vs. 5.0 [3.63 – 5.73] vs. 5.73 [3.77 – 5.73] vs. 5.73 [3.77 – 5.73] vs. 6.28 [4.04 – 5.00] vs. 6.28 [4.04 – 5.00] vs. <0.001
- Cardiac autonomic neuropathy: 36/167 (22) vs. 36/167 (22), 36/167 (22), 36/167 (22), 36/167 (22), 36/167 (22), 36/167 (22), 36/167 (22), <0.001
- Peripheral neuropathy: 58/220 (26) vs. 66/189 (35) vs. 33/108 (31) vs. 28/85 (33), 0.268

Data are n (%), mean ± sd, or median [IQR]. AER, albumin excretion rate; CSII, continuous subcutaneous insulin infusion; DBP, diastolic blood pressure; HbA1c, glycosylated hemoglobin; SBP, systolic blood pressure; SDS, standard deviation score; SES, socioeconomic status.

From a prognostic standpoint, we have demonstrated a more complete and informative assessment of both glycemic control and complications risk can be obtained by also considering a measure of glycemic variability. Moreover, although this was not an intervention study, we found the use of intensive insulin therapy was strongly associated with lower glycemic variability. This implies intensive regimens may provide additional protection beyond their role in reducing HbA1c and extends our previous observations that intensive insulin therapy is associated with a lower risk of microvascular complications in adolescents (12) (38). The possibility of dual protection is appealing as reduction of HbA1c alone is difficult in practice, with fewer than half of all patients able to maintain levels below the pediatric target of 7.5% (58 mmol/mol) (37).

Our findings may be limited by several factors. Firstly, the number of measurements per patient varied, so to minimize this potential bias, we divided SD-HbA1c by a function of the number of measurements. Future studies may also extend the analysis to include short-term glucose variability as well. SD-HbA1c in regression models may have artificially inflated the significance of one, or both, of these variables. Thirdly, there were fewer patients included in the analysis of CAN as HRV testing was only available in more recent years. However, it is unclear how this temporal bias could have systematically favored an association between glycemic variability and CAN.

Further research is required to elucidate the precise mechanisms mediating the association between HbA1c variability and complications risk, and to clarify why studies investigating short-term glucose variability have produced discrepant results. Future studies may also extend...
our endpoints to include markers of macrovascular disease. A recent meta-analysis of randomized controlled trials (RCTs) showed multiple daily injection therapy and continuous subcutaneous insulin infusion pumps provide similar HbA1c reduction in adolescents with type 1 diabetes (39). For our findings to be of direct clinical benefit, the mode of insulin delivery that best stabilizes HbA1c and reduces complications risk need to be identified.

Table 2. Generalized estimating equations for factors associated with microvascular complications in adolescents with type 1 diabetes

<table>
<thead>
<tr>
<th>Factors and outcome</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Retinopathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration</td>
<td>1.11 (1.08 – 1.15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>1.09 (1.04 – 1.14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP SDS</td>
<td>1.19 (1.07 – 1.31)</td>
<td>0.001</td>
</tr>
<tr>
<td>Height SDS</td>
<td>0.85 (0.77 – 0.93)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean HbA1c</td>
<td>1.88 (1.63 – 2.17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SD-HbA1c</td>
<td>1.32 (1.00 – 1.73)</td>
<td>0.049</td>
</tr>
<tr>
<td>CV (SD-HbA1c/Mean HbA1c)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Albinurina</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP SDS</td>
<td>1.32 (1.05 – 1.68)</td>
<td>0.019</td>
</tr>
<tr>
<td>Mean HbA1c</td>
<td>1.54 (1.20 – 1.97)</td>
<td>0.001</td>
</tr>
<tr>
<td>SD-HbA1c</td>
<td>1.81 (1.04 – 3.14)</td>
<td>0.036</td>
</tr>
<tr>
<td>CV (SD-HbA1c/Mean HbA1c)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Log10AER</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.93 (0.90 – 0.96)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>1.02 (1.01 – 1.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height SDS</td>
<td>1.02 (1.00 – 1.03)</td>
<td>0.016</td>
</tr>
<tr>
<td>Mean HbA1c</td>
<td>1.03 (1.01 – 1.06)</td>
<td>0.003</td>
</tr>
<tr>
<td>SD-HbA1c</td>
<td>1.10 (1.05 – 1.15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CV (SD-HbA1c/Mean HbA1c)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cardiac Autonomic Neuropathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.21 (1.09 – 1.34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP SDS</td>
<td>1.24 (1.01 – 1.52)</td>
<td>0.041</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>1.36 (1.08 – 1.72)</td>
<td>0.008</td>
</tr>
<tr>
<td>Mean HbA1c</td>
<td>1.28 (0.97 – 1.69)</td>
<td>0.080</td>
</tr>
<tr>
<td>SD-HbA1c</td>
<td>2.28 (1.23 – 4.21)</td>
<td>0.009</td>
</tr>
<tr>
<td>CV (SD-HbA1c/Mean HbA1c)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Peripheral Neuropathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.15 (1.07 – 1.24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>0.61 (0.45 – 0.84)</td>
<td>0.002</td>
</tr>
<tr>
<td>Height SDS</td>
<td>1.55 (1.32 – 1.81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI SDS</td>
<td>1.23 (1.01 – 1.50)</td>
<td>0.036</td>
</tr>
<tr>
<td>Mean HbA1c</td>
<td>1.19 (0.95 – 1.49)</td>
<td>0.122</td>
</tr>
<tr>
<td>SD-HbA1c</td>
<td>1.00 (0.63 – 1.60)</td>
<td>0.997</td>
</tr>
<tr>
<td>CV (SD-HbA1c/Mean HbA1c)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Both models adjusted for age (years), sex, diabetes duration (years), systolic blood pressure (SDS), diastolic blood pressure (SDS), cholesterol (mmol/liter), height (SDS), BMI (SDS) and socioeconomic disadvantage. AER, albumin excretion rate; CV, coefficient of variation; DBP, diastolic blood pressure; HbA1c, glycosylated hemoglobin; SBP, systolic blood pressure; SD-HbA1c, standard deviation of glycosylated hemoglobin; SDS, standard deviation score.

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Address all correspondence and requests for reprints to: Corresponding Author: Professor Maria E Craig, Institute of Endocrinology and Diabetes, The Children’s Hospital at Westmead, Locked Bag 4001, Westmead 2145, New South Wales, Australia; E-mail: m.craig@unsw.edu.au; Phone: +61298453907; Fax:
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"Quasi Likelihood Under Independence Model Criterion\(^{a}\)

\begin{tabular}{|l|c|c|c|}
\hline
Outcome & Reference Model\(^{b}\) & Model with sd-HbA\(_1c\), & Model With CV \(\text{sd-HbA}_{1c}/\text{Mean HbA}_{1c}\) \\
\hline
Retinopathy & 3821.6 & 3818.9 & 3817.4 \\
Albuminuria & 1074.4 & 1070.5 & 1070.7 \\
Cardiac Autonomic Neuropathy & 832.7 & 826.0 & 825.4 \\
Peripheral Neuropathy & 684.1 & 685.7 & 685.5 \\
\hline
\end{tabular}

\(^{a}\)Model criterion are in smaller-is-better form; \(^{b}\)Reference model includes age (years), sex, diabetes duration (years), systolic blood pressure (SDS), diastolic blood pressure (SDS), cholesterol (mmol/liter), height (SDS), BMI (SDS) and socioeconomic disadvantage; \(\text{sd-HbA}_{1c}\), standard deviation of glycemic variability; CV, coefficient of variation

+61298453170. Reprint requests should be addressed to cor-
responding author.

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terpretation and revised the manuscript. Y.H.C and P.B. con-
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Table 3. Goodness of fit statistics of generalized estimating equations assessing factors associated with microvascular complications in adolescents with type 1 diabetes

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