A1C Variability as an Independent Risk Factor for Microalbuminuria in Young People With Type 1 Diabetes

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OBJECTIVE—To assess the potential association between A1C variability (A1C-SD) and microalbuminuria in young people with type 1 diabetes.

RESEARCH DESIGN AND METHODS—Serially collected samples for A1C measurement were available for 1,232 subjects with childhood-onset type 1 diabetes recruited to the Oxford Regional Prospective Study and the Nephropathy Family Study.

RESULTS—The median (range) number of A1C assessments was 4 (2–16). Mean intrapersonal A1C was 9.5% and A1C-SD was 0.91. Mean A1C and A1C-SD values were higher in subjects with microalbuminuria ($n = 227$) than in those with normoalbuminuria (10.3 vs. 9.4%; 1.12 vs. 0.86, $P < 0.001$). In a Cox regression model, A1C-SD was independently associated with microalbuminuria (hazard ratio 1.31 [95% CI 1.01–1.35]).

CONCLUSIONS—In the current study, A1C variability was an independent variable that added to the effect of A1C on the risk for microalbuminuria in youth with type 1 diabetes, a population highly vulnerable to vascular complications.

Diabetes Care 34:1011–1013, 2011

Landmark studies, such as the Diabetes Control and Complications Trial (DCCT) and the Epidemiology of Diabetes and its Complications (EDIC), showed the importance of good glycemic control, as expressed by A1C values within normal reference ranges, in reducing the risk of vascular complications (1,2). Recent data from the DCCT and Finnish Diabetic Nephropathy (FinnDiane) study highlight an additional component of glycemic control, represented by A1C variability, independently associated with complication risk in type 1 diabetes (3,4).

A1C variability, expressed as the intrapersonal SD of serially measured A1C, is considered an index of long-term glycemic variability (3–5). Up to now, however, the relationship between A1C variability and vascular complications has not been assessed in young people with diabetes. It would be of interest to understand whether this parameter has an independent role in this group, where complication risk can be even higher than in adults and is associated with distinct risk factors such as puberty (6). Therefore, the aim of this study was to assess whether A1C variability was associated with microalbuminuria in young people with type 1 diabetes.

RESEARCH DESIGN AND METHODS

The study population consisted of 1,232 participants in the Oxford Regional Prospective Study (ORPS, $n = 418$) and Nephropathy Family Study (NFS, $n = 814$) with more than one A1C assessment, representing 84% of the whole cohorts. No participants were receiving treatment with any drug apart from insulin. Ethical approval was obtained from the district ethics committee, with written consent from the parents and assent from the children.

Between 1986 and 1996, the ORPS recruited children diagnosed with type 1 diabetes aged <16 years in the geographic region of the Oxford Health Authority (7). Between 2000 and 2005, the NFS recruited adolescents aged 10–16 years with type 1 diabetes throughout England (8).

Both cohorts have been monitored with annual assessments of A1C and the albumin/creatinine ratio (ACR). Microalbuminuria was defined as an ACR of between 3.5 and 35 mg/mmol in males and between 4.0 and 47 mg/mmol in females in two of three consecutive early morning urine samples (7,8) and was considered "persistent" when detected for ≥2 consecutive years or "transient" when present for 1 year with subsequent regression.

All urine samples were assessed centrally, as previously reported (7,8). A1C from ORPS was analyzed centrally, initially by an electrophoretic method (Ciba Corning Diagnostics, Halstead, U.K.) and then by high-performance liquid chromatography (Bio-Rad, Hemel Hempstead, U.K.), with DCCT-aligned methods (9). A1C from NFS was analyzed centrally on a Tosoh G7 Analyzer (Redditch, U.K.) using high-performance liquid chromatography and absorbance change detection and DCCT-aligned methods (8).

For each patient, the intrapersonal SD for A1C (A1C-SD) was calculated as the mean of all available A1C measurements until the age of 25 years. For subjects with microalbuminuria, only A1C measurements before the onset of this complication were included. An adjusted SD (adj-A1C-SD = $SD/\sqrt{[n/(n-1)]}$) was calculated to adjust for a different number of assessments among patients (3).

Data are expressed as mean ± SD or median (interquartile range [IQR]). Unpaired *t* test and ANOVA with Bonferroni post hoc test were used for comparisons between groups. A Cox regression analysis was performed to assess the association

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Received 26 October 2010 and accepted 23 January 2011.
DOI: 10.2337/dc10-2028
This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc10-2028/-/DC1.

between A1C-SD and microalbuminuria. Analyses were performed using SPSS 16 software (SPSS Inc., Chicago, IL).

RESULTS—The study population included 1,232 patients (683 boys; Supplementary Data). Their median (IQR) age at diagnosis was 9.2 (5.7–11.7) years, and diabetes duration at last A1C assessment was 8.6 (5.6–11.6) years. These participants were not dissimilar from the rest of the cohorts for male percentage (55%), age at diagnosis (9.6 [6.0–11.9] years), and duration of diabetes at the last visit (8.5 [5.5–11.9] years). The median (range) number of A1C assessments was four (2–16), mean A1C was 9.5% (ORPS: 9.8; NFS: 9.4), A1C-SD was 1.05 (ORPS: 1.27; NFS: 0.94), and adj-A1C-SD was 0.91 (ORPS: 1.15; NFS: 0.78).

Mean A1C and adj-A1C-SD were higher in the 227 subjects who developed microalbuminuria than in those with normoalbuminuria (10.4 vs. 9.4%; 1.16 vs. 0.86, $P < 0.001$). Similar differences were found when the ORPS (A1C: 10.5 vs. 9.6% [$P < 0.001$]; adj-A1C-SD: 1.32 vs. 1.10 [$P < 0.001$]) and NFS (A1C: 10.0 vs. 9.3% [$P < 0.001$]; adj-A1C-SD: 0.91 vs. 0.76 [$P = 0.005$]) cohorts were analyzed separately. After dividing the microalbuminuric group in persistent ($n = 82$) and transient ($n = 145$) subgroups, A1C and adj-A1C-SD were different between normoalbuminuric versus persistent (9.4 vs. 10.7% and 0.9 vs. 1.3 [$P < 0.001$]) and transient microalbuminuric (A1C: 10.2%; adj-A1C-SD: 1.1 [$P < 0.001$]), but not between the persistent and transient microalbuminuric patients. In a Cox regression model, adj-A1C-SD was independently associated with microalbuminuria (Table 1).

Table 1—*Cox regression model for the development of microalbuminuria: influence of A1C-SD alone (model 1), mean A1C alone (model 2), and their combined effect (model 3)*

Model	Hazard ratio (95% CI)	*P*
Model 1		
A1C-SD	2.06 (1.63–2.59)	<0.001
Model 2		
Mean A1C	1.43 (1.32–1.55)	<0.001
Model 3		
A1C-SD	1.31 (1.01–1.35)	0.04
Mean A1C	1.41 (1.28–1.54)	<0.001

Duration of diabetes was the time variable in the Cox proportional hazards model. Model 3 is adjusted for sex (1.32 [0.97–1.79]), age at diagnosis (1.28 [1.21–1.35]), and chronologic age (0.90 [0.84–0.96]). Results shown are hazard ratios for every 1-unit increase in each covariate.

CONCLUSIONS—In the current study, A1C variability was independently associated with microalbuminuria in young patients with childhood-onset type 1 diabetes. These results are in line with those from adult studies, where A1C variability was associated with nephropathy, retinopathy, and cardiovascular risk (3–5).

Some have suggested that A1C variability, reflecting long-term glycemic variability, may be linked to vascular complications by increasing oxidative stress (13). This is supported by the finding that glucose fluctuations induce oxidant production, and this effect appears to be even stronger than that caused by stable high-glucose values (10,11). The role of oxidative stress in the pathogenesis of vascular complications is well known and is suggested as the final mediator of several hyperglycemia-activated pathways (12). However, the association between A1C variability and vascular complications might be explained by other unknown mechanisms, which need to be explored in future studies.

These results highlight the concept that a good, stable glycemic control is of paramount importance and must be established early in the course of diabetes. Recent updated data from the EDIC study showed that the so-claimed metabolic memory, expression of earlier glycemic control, can wear off in the long-term, particularly in young people, and glycemic control during the earlier DCCT was the main determinant of this phenomenon (13). Therefore, young people with diabetes should be strongly encouraged to achieve a good glycemic control, to keep it over time, and to avoid even short periods of hyperglycemia.

A main strength of this study is the large sample size and the prospective design, which allowed the availability of a large number of samples for A1C assessment. Another strength is the central assessment of all A1C assays. In contrast, a potential limitation was the use of different methods to assess A1C in the two cohorts.

Further studies in youth with type 1 diabetes would likely replicate the results of this study and extend the investigation to other complications of diabetes.

Acknowledgments—The ORPS is funded by Diabetes UK. The NFS is funded by the Juvenile Diabetes Research Foundation, the Wellcome Trust, and Diabetes UK.

No potential conflicts of interest relevant to this article were reported.

M.L.M. researched and analyzed data and wrote the manuscript. R.N.D. researched data and contributed to discussion. F.C. contributed to discussion and reviewed and edited the manuscript. D.B.D. designed the study, contributed to discussion, and reviewed and edited the manuscript.

The authors acknowledge the study field workers, pediatricians, physicians, and diabetes nurse specialists involved in the ORPS and the NFS, and the National Institute for Health Research Cambridge Comprehensive Biomedical Research Centre.

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