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

L andmark 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). Microbuminuria 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

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).

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

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.

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.

References
1. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–986
2. Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. JAMA 2002;287:2563–2569
3. Kilpatrick ES, Rigby AS, Atkin SL. A1C variability and the risk of microvascular complications in type 1 diabetes: data from the Diabetes Control and Complications Trial. Diabetes Care 2008;31:2198–2202
4. Wadén J, Forsblom C, Thorn LM, Gordin D, Saraheimo M, Groop PH. A1C variability predicts incident cardiovascular events, microalbuminuria, and overt diabetic nephropathy in patients with type 1 diabetes. Diabetes 2009;58:2649–2655
5. Prince CT, Becker DJ, Costacou T, Miller RG, Orchard TJ. Changes in glycaemic control and risk of coronary artery disease in type 1 diabetes mellitus: findings from the Pittsburgh Epidemiology of Diabetes Complications Study (EDC). Diabetologia 2007;50:2280–2288
6. Marcovecchio ML, Tossavainen PH, Dunger DB. Prevention and treatment of microvascular disease in childhood type 1 diabetes. Br Med Bull 2010;94:145–164
7. Amin R, Widmer B, Prevost AT, et al. Risk of microalbuminuria and progression to macroalbuminuria in a cohort with childhood onset type 1 diabetes: prospective observational study. BMJ 2008;336:697–701
8. Marcovecchio ML, Dalton RN, Schwarze CP, et al. Ambulatory blood pressure measurements are related to albumin excretion and

are predictive for risk of microalbuminuria in young people with type 1 diabetes. Diabetologia 2009;52:1173–1181

9. Schultz CJ, Konopelska-Bahu T, Dalton RN, et al.; Oxford Regional Prospective Study Group. Microalbuminuria prevalence varies with age, sex, and puberty in children with type 1 diabetes followed from diagnosis in a longitudinal study. Diabetes Care 1999;22: 495–502

10. Monnier L, Mas E, Ginet C, et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. JAMA 2006;295:1681–1687

11. El-Osta A, Brasacchio D, Yao D, et al. Transient high glucose causes persistent epigenetic changes and altered gene expression during subsequent normoglycemia. J Exp Med 2008;205:2409–2417

12. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature 2001;414:813–820

13. White NH, Sun W, Cleary PA, et al.; DCCT-EDIC Research Group. Effect of prior intensive therapy in type 1 diabetes on 10-year progression of retinopathy in the DCCT/EDIC: comparison of adults and adolescents. Diabetes 2010;59:1244–1253