Commonly Measured Clinical Variables Are Not Associated With Burden of Complications in Long-standing Type 1 Diabetes: Results From the Canadian Study of Longevity in Diabetes

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Twenty-five percent of individuals with long-standing type 1 diabetes (T1D) are resistant to complications, and this is not entirely explained by superior glycemic control (1–4). Although associations between clinical variables and individual complications have been comprehensively examined (1–4), analysis of total complication burden may detect previously unrecognized associations.

The Canadian Study of Longevity in Diabetes actively recruited 325 individuals who had T1D for 50 or more years (5). Subjects completed a questionnaire, and recent laboratory tests and eye reports were provided by primary care physicians and eye specialists, respectively.

Nephropathy was defined by an albumin-to-creatinine ratio of >2 mg/mmol for participants on an ACE inhibitor or angiotensin receptor blocker (ARB) or >3.4 mg/mmol for participants not on an ACE inhibitor or ARB. Symptomatic neuropathy was defined by a score ≥ 3 on the Michigan Neuropathy Screening Instrument (MNSI) questionnaire component. Retinopathy was defined by documentation of nonproliferative or proliferative retinopathy in the eye specialist report. Coronary artery disease was defined by self-reported diagnosis or by angina, angioplasty, or coronary artery bypass, and peripheral vascular disease was defined by self-reported diagnosis or leg angioplasty or leg bypass. Thirty-six participants had incomplete documentation of one complication, and five participants had incomplete documentation of two complications. The burden of complications was defined as the sum of complications per individual proportionate to the total documented number of complications.

Multivariable Poisson regression was used and exposure was standardized using T1D duration as an offset. Variables were selected using a univariable screening approach. An α (type 1 error; two-tailed) threshold of <0.05 was used. All statistical analyses were performed using SAS 9.4 software.

The 325 participants were 65.5 ± 8.5 years old with diagnosis at age 10 years (interquartile range [IQR] 6.0, 16) and duration of 54.9 ± 6.4 years. Insulin dose was 0.5 units/kg (IQR 0.4, 0.6), and 44% of participants were male. The median burden of complications was 2.0 (IQR 1.0, 3.0) out of the possible 5. In univariable analyses, the following were significantly associated with a greater burden of complications: presence of hypertension, statin, aspirin and ACE inhibitor or ARB use, higher Problem Areas in Diabetes (PAID) and Geriatric Depression Scale (GDS) scores, and higher levels of triglycerides and HbA_{1c}. The following were significantly associated with a lower burden of complications: current physical activity, higher quality of life, and higher HDL cholesterol.

In the multivariable analysis, a higher PAID score was associated with a greater burden of complications (risk ratio [RR] 1.15 [95% CI 1.06–1.25] for each 10-point-higher score). Aspirin and statin use were also associated with a greater burden of complications (RR 1.24 [95% CI 1.01–1.52] and RR 1.34 [95% CI 1.05–1.70], respectively) (Table 1), whereas HbA_{1c} was not.

Our findings indicate that in individuals with long-standing T1D, burden of complications is largely not associated with historical characteristics or simple objective measurements, as associations with statistical significance likely reflect reverse causality. Notably, HbA_{1c} was not associated with burden of complications, which is similar to findings of no association between glycemic control and individual complications (1,3). This further confirms that other

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Table 1—Adjusted RRs for sum of complications from multivariable Poisson regression†

Predictor	Adjusted RR (95% CI)*	*P* value
Age	1.01 (0.99–1.02)	0.3
Male sex (ref. female)	1.00 (0.82–1.21)	1.0
HbA_{1c}	1.08 (0.98–1.18)	0.1
Hypertension (yes vs. no)	1.21 (0.99–1.47)	0.06
Triglycerides	1.16 (0.99–1.36)	0.06
PAID score‡	1.15 (1.06–1.25)	0.0009
Physically active (yes vs. no)	0.91 (0.74–1.12)	0.4
Frequency of minor hypoglycemia in past year		
Weekly	Ref.	—
Monthly	1.01 (1.01–1.02)	0.4
Less than monthly	0.89 (0.70–1.14)	0.06
Infrequent	0.73 (0.52–1.02)	0.8
Aspirin (yes vs. no)	1.24 (1.01–1.52)	0.04
Statin (yes vs. no)	1.34 (1.05–1.70)	0.02

Omnibus likelihood ratio χ^2(df)=137.3(12), $P < 0.0001$. *RR reported for 1-unit increase in continuous variables, unless specified otherwise. †Model based on $n = 251$. ‡For increase in PAID score of 10 points.

unmeasured variables such as genetic, metabolic, or physiologic characteristics may best identify mechanisms and biomarkers of complications in longstanding T1D.

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