

RESEARCH UPDATE

2009 Operating Grant Recipient, Dr. Denis Daneman

The Canadian Diabetes Association offers support for research projects designed to enhance our knowledge of the prevention, etiology, management, and cure of diabetes and related complications, as well as population health, health services, diabetes education, community and practice-based research.

Dr. Denis Daneman is Paediatrician-in-Chief at the Hospital for Sick Children and Chair of the Department of Paediatrics at the University of Toronto. His clinical work is focused on care of children and adolescents with diabetes, and care of children with endocrine disorders. His research focuses on factors affecting metabolic control and the early onset of complications in children and adolescents with type 1 diabetes. In 2009, Dr. Daneman was awarded a 3-year Canadian Diabetes Association operating grant, for the Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial (AdDIT).

Previously, Dr. Daneman and his colleagues identified that, if microalbuminuria is present within 10 years of diagnosis in adolescents, it will progress to diabetic nephropathy within the next 10 years in two-thirds of these patients. Findings also suggest that metabolic control (assessed by glycated hemoglobin [A1C]) influences the occurrence, persistence or progression of microalbuminuria. This underlies the need to start screening for microalbuminuria early in adolescents with type 1 diabetes and the need for maintenance of good metabolic control (1).

In 2007, Dr. Daneman and colleagues determined that higher than average albumin excretion during early puberty, combined with an elevated A1C, is predictive of subsequent risk for the development of microalbuminuria. Given that microalbuminuria is itself a marker for progression to nephropathy in type 1 diabetes, it may be possible to identify adolescents at future risk for diabetic nephropathy using an albumin excretion phenotype (2).

It is important to find ways to delay progression to nephropathy in people with diabetes. Nephropathy is one of the most common complications of diabetes, and diabetic nephropathy is the leading cause of kidney failure in Canada. In addition, a person with diabetic nephropathy is among those at highest risk for cardiovascular (CV) morbidity and mortality (3).

Currently, treatment is indicated only for those adolescents with persistent microalbuminuria (3). One short-term

randomized controlled trial in adolescents with type 1 diabetes demonstrated that angiotensin-converting enzyme (ACE) inhibitors were effective in reducing microalbuminuria compared to placebo (4). Increasingly, adolescents with persistent microalbuminuria are being treated with ACE inhibitors because this treatment has been shown to reduce the risk of progression to nephropathy and may be effective at reducing CV complications in adults. However, there are no long-term intervention studies that have examined whether ACE inhibitors or angiotensin II receptor antagonists could delay the progression to nephropathy in adolescents with microalbuminuria (3).

Throughout the AdDIT trial, Dr. Daneman and his colleagues hope to address this clinical uncertainty. This is an international trial being carried out in the United Kingdom, Australia and Canada. Dr. Daneman is heading the Toronto portion of this study. The Toronto co-investigators in the trial include Drs. Jacqueline Curtis, Farid Mahmud and Etienne Sochett, all members of the Division of Endocrinology, at the Hospital for Sick Children and University of Toronto.

The trial will determine whether early therapy (statin, ACE inhibitor or a combination of both) is effective in reducing future complications of diabetic nephropathy and cardiovascular disease (CVD) in adolescents with childhood-onset type 1 diabetes. Specifically, Dr. Daneman and his team will determine if treatments improve risk factors for nephropathy by: reducing albumin excretion, assessed every 6 months by measuring morning urine albumin/creatinine ratio; reducing the incidence of microalbuminuria in two of three urine samples; and reducing the incidence of microalbuminuria during 6 months after the intervention phase of the trial.

This team will also look at the effect of these medications on other CV complications of diabetes, including measuring arterial wall thickness (an early indicator of CVD); monitoring blood pressure, lipids and lipoproteins; screening for retinopathy; monitoring glomerular filtration rate; assessing changes to CVD risk biomarkers; examining quality of life, risk-benefit, compliance and health economic assessment; and monitoring long-term outcomes with regard to incidence of diabetic nephropathy and CVD.

Dr. Daneman anticipates this study will show that ACE inhibitors, statins and combination ACE inhibitor/statin

therapy will reduce albumin excretion and microalbuminuria. He and his team anticipate that the therapies will also improve CVD risk factors and early CVD risk markers, and improve quality of life, with the greatest effect anticipated with combination therapy. It is hoped that this study will lead to early identification and intervention of adolescents with type 1 diabetes at high-risk for diabetic nephropathy and CVD, and could lead to long-term improvements in prognosis.

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