Cardiovascular Disease Protection in Long-Duration Type 1 Diabetes and Sex Differences

Diabetes Care 2015;38:e73–e74 | DOI: 10.2337/dc15-0017

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Two recent articles describe higher morbidity and mortality from cardiovascular disease (CVD) at younger ages for women with type 1 diabetes compared with men in cohorts with average duration of approximately 30 years (1,2). Women in the Joslin 50-Year Medalist Study (total $n = 680$) have a significantly lower CVD prevalence than men (women 35.3% vs. men 51.6%, $P < 0.001$), suggesting a protective factor. The objective of this analysis was to investigate protective factors associated with CVD and sex-associated differences in rates in those with long-term type 1 diabetes.

The Joslin 50-Year Medalist Study is a cross-sectional study of individuals with 50 or more years of type 1 diabetes ($n = 651$). To be awarded the Joslin 50-Year Medal, individuals provide an original medical record from time of diagnosis, or three other forms of documentation of insulin dependence since the time of diagnosis 50 or more years before the date of application for the medal. Participants underwent a clinical exam, biospecimen collection and completed a medical history questionnaire that included assessment of physical activity. CVD status was based on self-reported history of coronary artery disease, angina, heart attack, prior cardiac or leg angioplasty, or bypass graft surgery of participants (3); several studies have demonstrated the reliability and validity of self-reported heart disease (4). Physical activity patterns were verified in a subset (514/668) by the Paffenbarger College Alumnus Questionnaire (5). Participants had a median [Q1, Q3] age of 69 [64, 76] years, disease duration of 57 [54, 62] years, and age at diagnosis of 11 [6, 15] years. Median A1C in this population was 7.0% [6.5, 7.6] (53.0 [47.5, 59.6] mmol/mol) and BMI was 24.8 kg/m^2. Use of antihypertensive and lipid-lowering medications was reported by 82.3% and 67.7% of Medalists, respectively. Diabetic nephropathy (DN) (estimated glomerular filtration rate <45 mL/min/1.73 m^2) was found in 14.9% of the Medalists.

In multivariable analyses HDL-C (odds ratio [OR] [adjusted for age and DN] 0.98, 95% CI 0.97, 0.99) eliminated the effect of sex with sufficient power present. Data on subfractions of HDL-C, apolipoprotein AI and AII in a subset of men (64/304) and women (71/331) indicates higher levels in women without CVD compared to those with CVD, suggesting a mechanism by which elevated HDL-C may be protective in this cohort (women: apolipoprotein AI median [Q1, Q3]: no CVD 156 [140, 171] vs. CVD 144 [129–151] mg/dL, $P = 0.007$; apolipoprotein AII: no CVD 31 [29–34] vs. CVD 28 [26–32] mg/dL, $P = 0.02$). Due to the known effects of exercise on HDL-C, we hypothesized a relationship between this cholesterol, exercise, and CVD among female Medalists in this physically active cohort. In multivariable sex-stratified models, a significant effect by physical activity on the odds of CVD was found in male Medalists (age, A1C, DN-adjusted OR: 0.25 [0.12, 0.52]), but not in female Medalists (adjusted OR 1.1 [0.6, 2.1]).

These data indicate some female patients with type 1 diabetes may be protected from CVD. Elevating HDL-C among women and increasing physical activity in men may significantly decrease the odds of CVD in aging patients with type 1 diabetes. These data have important clinical implications due to recent findings of increased risk of heart disease among women with type 1 diabetes and the increasing age of the type 1 diabetic cohort.

Acknowledgments. The authors wish to express their appreciation for the support provided by the Clinical Research Center at the Joslin Diabetes Center.

Funding. The Joslin Medalist Study is supported by the National Institute of Diabetes and Digestive and Kidney Diseases (P30DK036836, UL1 RR025758-03, R24 DK083957-01, DP3 DK094333-01), JDRF (17-2013-310), and contributions by Mr. Tom Beatson and many Medalists. In addition, Z.H.H. is a recipient of the National Institute of Diabetes and Digestive and Kidney Diseases T32 training grant (T32DK007260).

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The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.
Author Contributions. Z.H.H., S.A.D., L.J.T., S.M.H., G.L.K., and H.A.K. contributed to data collection, analysis, and writing and editing assistance. S.F. contributed to data collection, analysis, and writing assistance. M.K. contributed to writing and editing assistance. J.K.S., S.J.T., and E.J.S. contributed to data collection. H.A.K. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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