Social Determinants of Health Are Associated with Markers of Renal Injury in Adolescents with Type 1 Diabetes

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Objective To examine the relationship between the social determinants of health and markers of early renal injury in adolescent patients with type 1 diabetes (T1D).

Study design Renal outcomes included estimated glomerular filtration rate (eGFR) and albumin–creatinine excretion ratio (ACR). Differences in urinary and serum inflammatory markers also were assessed in relation to social determinants of health. Regression analysis was used to evaluate the association between the Ontario Marginalization Index (ON-Marg) as a measure of the social determinants of health, patient characteristics, ACR, eGFR, and renal filtration status (hyperfiltration vs normofiltration).

Results Participants with T1D (n = 199) with a mean age of 14.4 ± 1.7 years and diabetes duration of 7.2 ± 3.1 years were studied. Mean eGFR was 122.0 ± 19.4 mL/min/1.73 m^2. Increasing marginalization was positively associated with eGFR ($P < .0001$) but not with ACR ($P = .605$). Greater marginalization was associated with greater median levels of urinary interleukin (IL)-2, IL-12 (p40), macrophage-derived chemokine, monocyte chemoattractant protein-3, and tumor necrosis factor-β and serum IL-2. ON-Marg was significantly associated with eGFR after we controlled for age, sex, body mass index z score, ethnicity, serum glucose, and hemoglobin A1c in linear regression. A similar association between hyperfiltration and ON-Marg score was observed in multivariable logistic regression.

Conclusion Increasing marginalization is significantly associated with both eGFR and hyperfiltration in adolescents with T1D and is associated with significant changes in urinary inflammatory biomarkers. These findings highlight a potentially important interaction between social and biological determinants of health in adolescents with T1D. *(J Pediatr 2018;■■:■■-■■).*

Diabetic nephropathy is associated with morbidity and mortality in patients with type 1 diabetes (T1D)[1] and will develop in approximately one-third of patients with T1D. Diabetic nephropathy is a progressive disease that begins with microalbuminuria and later progresses to overt nephropathy, rapid renal decline, and end-stage renal disease.[2] In this paradigm, microalbuminuria is a key indicator of subsequent risk of diabetic nephropathy. Newer studies have demonstrated that many patients with microalbuminuria do not progress and may even revert to normoalbuminuria.[3] Glomerular hyperfiltration is similarly considered a risk factor for the development of diabetic nephropathy[4] and is associated with early markers of renal injury, including albuminuria and increased urinary cytokine/chemokine excretion before the development of microalbuminuria.[5]

Beyond traditional physiological factors associated with diabetic kidney disease, social determinants of health have a powerful influence on outcomes.[6] The social determinants of health encompass "the conditions in which people are born, grow, work and age, and the systems put in place to deal with illness" and include factors such as education, income, and social status.[7] These factors are of particular importance during childhood, where exposure to social disadvantage can set young patients on a trajectory that can shape future health outcomes, persisting long into adulthood.[8-11] Most research in the field of social medicine has focused on early childhood exposures and experiences, yet adolescence is an equally critical developmental period that is highly sensitive to the effects

ACR	Albumin:creatinine ratio
AdDIT	Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial
BMI	Body mass index
eGFR	Estimated glomerular filtration rate
GFR	Glomerular filtration rate
HbA1c	Hemoglobin A1c
IL	Interleukin
MCP	Monocyte chemoattractant protein
MDC	Macrophage-derived chemokine
MIP-1α	Macrophage inflammatory protein-1α
ON-Marg	Ontario Marginalization Index
PDGF	Platelet-derived growth factor
T1D	Type 1 diabetes

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of social determinants of health.[9] Despite the growing repertoire of technological innovations in diabetes care, adolescents continue to exhibit suboptimal glycemic control compared with adults.[12] Adolescence is also a critical period for determining the lifetime risk of complications in T1D due to hormonal and metabolic changes and because the first signs of microvascular disease appear during this time.[13-16]

Many behavioral and biological outcomes in children with T1D track along a social gradient,[17] including poorer psychosocial functioning,[18] worsened glycemic control,[19,20] greater risk of acute complications including diabetic ketoacidosis and acute care use,[21] increased prevalence of modifiable cardiovascular risk factors, and early signs of cardiovascular dysfunction.[19] The goal of our study was to explore the relationships between social determinants of health and signs of early renal risk in pediatric patients with T1D. We also sought to examine potential differences in urinary and serum inflammatory markers in relation to social determinants of health as a potential biological mediator linking marginalization with early renal changes.

Methods

This study evaluated participant data from an existing cohort of adolescents with T1D from the observational arm of the Canadian Adolescent Diabetes Cardiorenal Intervention Trial (AdDIT),[22,23] linked to population-level census data from Ontario, Canada. Patient-level data were obtained from participants with T1D receiving care at the Hospital for Sick Children and affiliated regional diabetes care centers in Toronto, Ontario, who were enrolled in the observational arm of the AdDIT clinical trial. All data used for this study were obtained at the participants' baseline study visit. The Ontario Marginalization Index (ON-Marg) was used as an area-level measure of the social determinants of health. Ethics approval for the AdDIT study was granted through the Hospital for Sick Children institutional research ethics board.

Detailed descriptions of the AdDIT study population and methods have been published previously.[22,23] This population has also been shown to be representative of the greater Toronto population in terms of the social determinants of health.[24]

ON-Marg Measures

The ON-Marg is a census-based index developed to assess levels of marginalization across residential areas in Ontario, Canada. This measure has been validated across time and geographic areas and has proven to be a useful tool for the study of health disparities, being associated with numerous health outcomes.[25] The ON-Marg represents the average of 4 social determinants of health dimensions measured in quintiles, each representing 20% of the reference population (Q1: least marginalized; Q5: most marginalized).[26] The 4 dimensions include residential instability (ie, housing status, home ownership, etc), material deprivation (ie, education, unemployment, income, etc), ethnic concentration (ie, recent immigrants, visible minorities, etc), and dependency (ie, participation in labor force). Details of ON-Marg indicators, dimensions, and use are available from the ON-Marg User Guide.[26]

Primary and Secondary Outcomes

The primary outcomes of this study were markers of early renal injury, assessed by participants' baseline estimated glomerular filtration rate (eGFR) and albumin:creatinine ratio (ACR). eGFR was calculated via a combined cystatin-C and creatinine-based equation ($eGFR_{Zappitelli}$), which has demonstrated accuracy in estimating glomerular filtration rate (GFR) in various pediatric populations, including patients with and without renal disease.[27-29] ACR was determined based on 2 sets of 3 early morning urine samples.

The secondary outcome of this study was baseline inflammation, assessed by serum and urinary levels of 15 inflammatory markers. These markers were selected a priori from a list of 47 analytes previously measured as part of the AdDIT study and included eotaxin, fibroblast growth factor-2, interferon-α, interleukin (IL)-2, IL-6, and IL-12 (p40/p70), macrophage-derived chemokine (MDC), monocyte chemoattractant protein (MCP)-1, MCP-3, macrophage inflammatory protein-1α (MIP-1α), tumor necrosis factor (TNF)-α, TNF-β, Scd4-ligand (sCD40L), platelet-derived growth factor (PDGF)-AA, PDGF-BB, and regulated on activation, normal T-cell expressed and secreted (RANTES). Selection was based on analytes previously associated with hyperfiltration in similar populations[5,30,31] or with socioeconomic status.[32] Details regarding AdDIT study baseline biochemical and clinical assessments have been described previously.[22,23,31] Urinary cytokine values were adjusted for urine creatinine to account for differences in concentration. Biochemical data outside assay limits of detection were not included for statistical analysis.

Other Variables of Interest

Other variables included in our analysis as potential modifiers were sex, age at baseline, duration of T1D, ethnicity (white vs nonwhite), treatment regime (pump vs injection therapy), glycemic control (hemoglobin A1c [HbA1c]), height, weight, waist circumference, body mass index (BMI) z scores, lipids (high-density lipoprotein, low-density lipoprotein, triglycerides, cholesterol), blood pressure, and smoking status. All variables were recorded from baseline clinic visits.[22]

Although more detailed data regarding patient ethnicity were available (white, black, Chinese, South Asian, and other), ethnicity was dichotomized as white vs nonwhite, given the relatively small sample size of the other ethnic groups in this cohort. The low statistical power associated with the analysis of individual ethnic groups limited the opportunity to extrapolate meaningful conclusions from participant data, such that dichotomization of the ethnicity variable was used for analytical purposes.

Statistical Analyses

Statistical analysis was carried out with R Statistics v.3.1.2 (R Foundation for Statistical Computing, Vienna, Austria; www.R-project.org). Continuous characteristics were summarized by the use of summary statistics (mean ± SD); categorical variables were summarized with frequencies and percentages. The Pearson correlation was used to assess correlations between ON-Marg quintile scores and eGFR, ACR, and urinary/serum

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