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CARDEA study protocol: investigating early markers of cardiovascular disease and their association with lifestyle habits, inflammation and oxidative stress in adolescence using a cross-sectional comparison of adolescents with type 1 diabetes and healthy controls

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ABSTRACT

Introduction Little is known regarding associations between potentially modifiable lifestyle habits and early markers of cardiovascular disease (CVD) in pediatric type 1 diabetes (T1D), hindering early prevention efforts. Specific objectives are: (1) compare established risk factors (dyslipidemia, hypertension) with novel early markers for CVD (cardiac phenotype, aortic distensibility, endothelial function) in adolescents with T1D and healthy age-matched and sex-matched controls; (2) examine associations between these novel early markers with: (i) lifestyle habits; (ii) adipokines and measures of inflammation; and (iii) markers of oxidative stress among adolescents with T1D and controls, and determine group differences in these associations; (3) explore, across both groups, associations between CVD markers and residential neighbourhood features.

Methods and analyses Using a cross-sectional design, we will compare 100 participants aged 14–18 years with T1D to 100 healthy controls. Measures include: anthropometrics; stage of sexual maturity (Tanner stages); physical activity (7-day accelerometry); sleep and sedentary behaviour (self-report and accelerometry); fitness (peak oxygen consumption); and dietary intake (three non-consecutive 24-hour dietary recalls). Repeated measures of blood pressure will be obtained. Lipid profiles will be determined after a 12-hour fast. Cardiac structure/function: non-contrast cardiac magnetic resonance imaging (CMR) images will evaluate volume, mass, systolic and diastolic function and myocardial fibrosis. Aortic distensibility will be determined by pulse wave velocity with elasticity and resistance studies at the central aorta. Endothelial function will be determined by flow-mediated dilation. Inflammatory markers include plasma leptin, adiponectin, tumour necrosis factor alpha (TNF-α), type I and type II TNF-α soluble receptors and interleukin-6 concentrations. Measures of endogenous antioxidants include manganese superoxide dismutase, glutathione peroxidase and glutathione in blood. Neighbourhood features include built and social environment indicators and air quality.

Ethics and dissemination This study was approved by the Sainte-Justine Hospital Research Ethics Board. Written informed assent and consent will be obtained from participants and their parents.

Trial registration number NCT04304729.

Strengths and limitations of this study

- This is the first study designed to document associations between lifestyle habits and early markers of cardiovascular disease (CVD) risk among youth with type 1 diabetes (T1D) and compare these to healthy controls.
- We use validated, state-of-the-art measures of both lifestyle habits (eg, physical activity by accelerometry) and novel markers of CVD (eg, cardiac MRI).
- Our study is the first to examine the association between early CVD markers among youth with T1D and oxidative stress likely caused by intracellular redox modifications induced by the breakdown of the homeostasis of a non-radical molecule, hydrogen peroxide (H_2O_2), and not by the production of free radicals as is commonly undertaken.
- A challenge of this study will be the recruitment of healthy control adolescents that are of similar sociodemographic backgrounds as adolescents with T1D.
- We incorporate an environmental component, and will compare the associations between neighbourhood features (including built and social environments, air quality) and early markers of CVD across adolescents with T1D and healthy controls.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of mortality among individuals with type 1 diabetes (T1D),[1–3] with a 10–29-fold increased risk of CVD mortality compared with healthy controls.[3–7] Atherosclerosis begins in childhood, appearing to be more prevalent and aggressive in youth with T1D.[8–11] Nonetheless, little is known regarding the mechanisms underlying CVD risk or its early markers in youth with T1D, hindering efforts at early prevention. While adult CVD studies assess 'hard' endpoints such as myocardial infarcts, available surrogate measures most commonly studied in youth are traditional markers including lipids and blood pressure. Although dyslipidemia is common in children with T1D,[9 12–14] T1D may, even in the presence of normal lipid concentrations, be associated with more atherogenic lipid profiles,[15–18] that are strong predictors of incident CVD in adults,[19 20] and later CVD in children.[21 22] Similarly, hypertension in youth with T1D has been associated with the development of carotid thickening.[23 24] Dyslipidemia and hypertension appear to precede CVD in youth with T1D, however, no study to date has compared these markers to more sensitive markers of CVD in this population.

While studies measuring cardiac and vascular structure and function are gaining interest as surrogate measures of CVD risk in youth, data are sparse, with relatively small sample sizes, and generally stemming from young adults. Flow-mediated dilation appears to be impaired in youth with T1D[25 26] who may also have higher arterial stiffness.[27–29] Similarly, increased left ventricular (LV) septal thickness has been reported in youth with T1D,[30] with conflicting results regarding systolic dysfunction.[31–33] Despite the advantage of not exposing individuals to radiation, few studies to date have used cardiac magnetic resonance imaging (CMR) in youth with T1D. One exception is a small study focusing on aortic MRI in youth with T1D, which found that those with lower insulin sensitivity displayed lower aortic strain and distensibility.[34] Our study is the first to quantitatively assess early changes in myocardial morphology and function in a controlled population of adolescents with T1D using novel, sensitive methods, in addition to more traditional methods.

Despite the extensive evidence supporting the favourable impact of lifestyle habits on CVD in non-diabetic adults,[35] scant data exist in youth with T1D. Physical activity was reported to be inversely associated with coronary artery calcifications in both adults with and without T1D.[36] While there is some evidence linking physical activity to reduced CVD risk in youth with T1D,[37–40] studies are limited by generally small sample sizes and methodological shortcomings. Reduced aerobic capacity in both adults[41] and adolescents[42] with T1D has been documented, and this may be a precursor to cardiac diastolic dysfunction, at least in adults. There are no studies examining how sleep and sedentary behaviours are related to CVD risk in youth with T1D despite the declining duration of sleep[43] and increase in sedentary behaviour[44] among adolescents in general, and the adverse association between sedentary behaviour and CVD risk.[45 46] Moreover, evidence of the association between diet and CVD risk is sparse and largely inconclusive in healthy youth[47–50] and adults with T1D,[51 52] and is largely unstudied in children with T1D, despite their documented inadequate intake of fruits/vegetables and excessive intake of fat.[53]

Beyond lifestyle behaviours, inflammation is a critical factor leading to CVD in T1D. The classic inflammatory markers, including high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6) and tumour necrosis factor alpha (TNF-α), are elevated among individuals with T1D.[54] However, the high concentrations of adiponectin measured in adults with T1D are, to date, a paradox. Adiponectin, usually associated with more favourable insulin sensitivity, is on the contrary associated with insulin resistance and an increased risk of CVD in this population.[55 56] It is widely accepted that oxidative stress is caused by the production of free radicals. Nevertheless, as atherosclerosis develops from childhood, it is highly plausible that the presence of inflammation and the paradoxical role of adiponectin result, instead, from intracellular redox modifications induced by the breakdown of the homeostasis of a non-radical oxidative molecule that is hydrogen peroxide (H_2O_2), leading to the development of CVD.

In particular, the reactivity of H_2O_2 with the thiol groups of proteins leads to their inhibition, thus disturbing the sensitivity of the insulin receptor and possibly explaining the lack of effect of adiponectin on insulin sensitivity in the T1D population.[57] The reactivation of proteins oxidised by H_2O_2 is dependent on the cellular level of glutathione (GSH), the redox buffer of the cell, governing the oxidation state of thiol groups of proteins.[58] This oxidation phenomenon also explains the activation of NF-κB, a strong transcription factor essential for the induction and maintenance of inflammation.[59] Hyperglycemia, linked to the production of oxidizing molecules, can only exacerbate the deleterious impact of H_2O_2 on redox-sensitive signalling pathways. H_2O_2 homeostasis is dependent on its formation, mainly managed by manganese superoxide dismutase (MnSOD) from the mitochondria, and its reduction by GSH peroxidases, using GSH as cosubstrate.[60 61] Overall, few studies have examined the role of H_2O_2 homeostasis in the development of CVD risk among youth with T1D.

Although the role of neighbourhood environment factors on CVD has been extensively studied among general adult populations,[62] much less is known about environmental factors in relation to CVD risk among youth with T1D. Of the available studies, most have contributed evidence towards an inverse association between neighbourhood-level socioeconomic status and glycemic control.[63–65] One study reported that residing in more socioeconomically deprived neighbourhoods was associated with greater arterial stiffness among youth with T1D.[64] Further, although the harmful effects of air pollution on CVD in adults have been demonstrated,[66] only two studies have examined this association among

youth with T1D, with conflicting results. While one study reported no association,[67] the other observed an unexpected inverse relation between ozone level and glycated hemoglobin (HbA1C).[68]

The main goal of our study (initiated January 2017) is to gain a better understanding of clinical CVD in youth with T1D, by using novel imaging technology to identify the earliest detectable abnormalities, and determining how these relate to lifestyle habits, inflammation and oxidative stress, and to neighbourhood characteristics. Our hypotheses are: (1) adolescents with T1D will have early morphological and functional abnormalities of the myocardium as assessed by CMR, with moderate correlation to more established markers (dyslipidemia, hypertension); (2) better lifestyle habits will be associated with fewer myocardial/endothelial abnormalities; (3) deleterious profiles in inflammatory markers, adipokines and H_2O_2 homeostasis will be detected in adolescents with T1D compared with controls, associated with abnormalities in myocardial/endothelial structure and function, irrespective of lifestyle habits and adiposity; and (4) adverse neighbourhood features will be more strongly associated with abnormalities in myocardial/endothelial structure and function among youth with T1D versus controls.

Our specific aims are to:

1. Compare established risk factors (dyslipidemia, hypertension) with novel early markers for CVD (cardiac phenotype, aortic distensibility, endothelial function) in adolescents with T1D and healthy age-matched and sex-matched controls;
2. Examine the associations between these novel early markers with: (i) lifestyle habits; (ii) adipokines and measures of inflammation; and (iii) markers of oxidative stress among adolescents with T1D and healthy age-matched and sex-matched controls, and determine group differences in these associations;
3. Explore, across both groups, the associations between these established and novel early markers of CVD with neighbourhood features.

METHODS AND ANALYSES

Study population

The Sainte-Justine University Health Center Diabetes Clinic is the largest paediatric diabetes centre in Quebec, Canada. Currently, the clinic follows close to 900 patients with T1D, with an additional 120 newly diagnosed patients with T1D each year. For the study, 100 adolescents are being recruited from the Diabetes Clinic if they have a diagnosis of T1D, are 14–18 years of age and have no other known pathology that would influence their risk for CVD (eg, congenital cardiomyopathy, etc). Children without a primary diagnosis of T1D (eg, youth with another type of diabetes such as T2D) or conditions that could limit their ability to participate in the study are excluded. We are also recruiting 100 healthy, age-matched and sex-matched controls from nearby schools. Several efforts to enhance recruitment have been put in place (eg, letter sent to potential participants, posters in the Diabetes Clinic waiting room, in addition to direct approach by a research assistant to invite youth to participate). We offer a small stipend to compensate for potential inconveniences as well. Data collection is intensified during the summer months, so as to avoid participants missing school.

Study design

This cross-sectional study serves as the foundational step to establish a unique prospective study of youth with T1D and healthy controls, with a comprehensive assessment of both cardiovascular risk and a wide-range of potential determinants, using state-of-the-art technology.

Procedures and measures

Interested families are invited to provide informed consent (parents) and assent (children), and attend a full day at the clinical research unit where data are collected (see patient timeline in figure 1). Accelerometry data are collected during the week following the clinical research visit. Dietary recalls are performed within 6–8 weeks of the clinical research visit. For participants with T1D, medical records are reviewed to extract information on the date of diagnosis, type of insulin treatment, daily insulin requirements, as well as results of screening for retinopathy, nephropathy and auto-immune diseases.

Clinical, biological, social and environmental determinants of interest to this study were selected on the basis of their potential or established link with CVD and/or with the fact that they are modifiable through preventive strategies.

Anthropometry, blood pressure and stage of sexual maturation

Height, weight, waist circumference, heart rate and blood pressure are measured according to standardised protocols.[69–71] BMI (kg/m^2) z-scores are calculated according to the WHO reference values.[72] Stage of sexual maturity is scored by trained nurses according to Tanner stages.[73 74]

Dietary intake

A dietician conducts three non-consecutive 24-hour diet recalls on different days of the week including 1 weekend day[75] within a 6–8-week period of the research visit. The mean of three recalls is used. This method has been used in several settings with good results in adults[76] and we have successfully used this method in close to 600 children.[77] The Canadian Nutrient File program (CANDAT, Godin and Assoc, London, Ontario, Canada) is used to calculate daily nutrient intake, and to ascertain nutrient content of groupings of similar foods (eg. regular or diet soft drinks).

Physical activity

Physical activity is assessed over a 7-day period using an Actigraph GT3X+ activity monitor (Actigraph LLC,

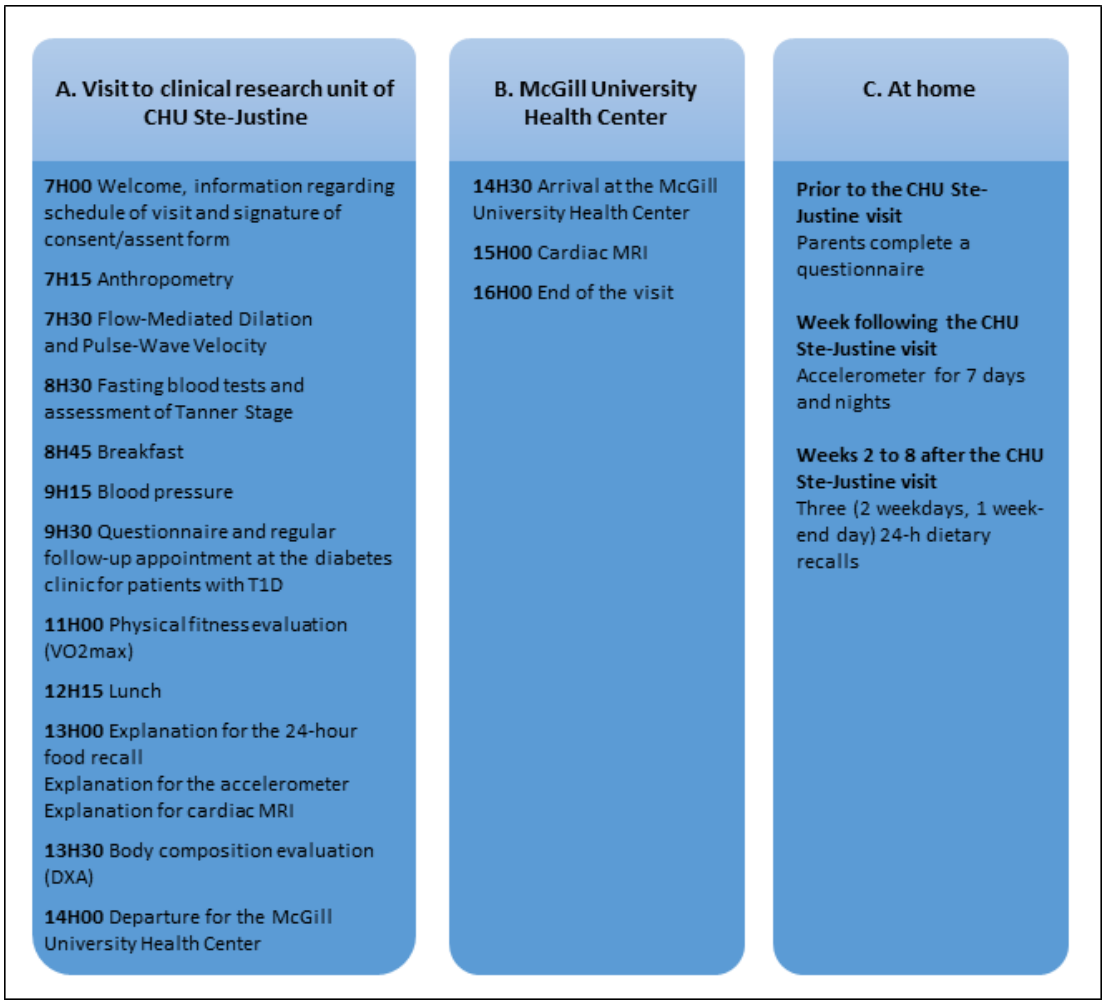

Figure 1 Schematic representation of patient timeline for data collection.

Pensacola, Florida, USA). Accelerometry data undergo standardised quality control and reduction procedures.[78] The recordings are considered valid when the accelerometer is worn for a minimum of 10 hours daily, for 4 or more days.[78] The average time spent daily in sedentary, light, moderate and vigorous physical activity is computed for each participant using validated pediatric cut-points.[79]

Fitness

Fitness is estimated using peak oxygen consumption (VO_2 peak), the gold standard in youth. VO_2 peak is determined during an adapted standard incremental exercise test,[80] on an electromagnetic bicycle, to volitional exhaustion, with indirect calorimetry measurements throughout the test.

Sedentary behaviour

Screen time is assessed using a self-administered questionnaire, documenting habitual daily hours of television viewing and leisure computer/tablet/video game use. Weekdays and weekends are addressed separately, and weighted average daily hours of leisure screen time are computed. Accelerometer-measured sedentary time is estimated using the average daily minutes at <100 counts based on accelerometer data.[79]

Sleep

The number of hours of sleep is based on self-report, as well as objectively measured using accelerometry,[81] which provides valid and reliable estimates of sleep time.[82]

Child health, biological parents' health history, and family socioeconomic position

Data are collected via questionnaire to ascertain potential confounders of the associations of interest. A self-administered questionnaire collects information on the participants' general health, including specific questions for the participants with T1D (eg, date of diagnosis of diabetes, type of insulin and method of administration, including injections versus pump). For participants with T1D, we record their daily insulin requirement from medical records (units/kg/day). A self-administered questionnaire for parents collects information on socioeconomic status (based on income and education), family history of hypertension, dyslipidemia, diabetes, CVD and obesity. The parent questionnaire is mailed to the parents, completed at home and verified for completeness on site

on the day of evaluation. With some exceptions, all questionnaire items were drawn from existing questionnaires in youth populations.

Blood chemistry

Blood samples are collected after participants have fasted for 12 hours overnight. A whole blood specimen is collected and stored at −80°C for analysis. Measures derived from plasma include glucose and lipids, with HbA1c measured from whole blood. Inflammatory markers include plasma leptin, adiponectin, TNF-α, type I and type II TNF-α soluble receptors and IL-6 concentrations.

Oxidative stress

The intracellular levels of H_2O_2 being very low (<1 µM), the endogenous regulation of hydrogen peroxide (H_2O_2) is estimated by measuring the levels of GSH (by capillary electrophoresis) and activities of GSH peroxidase (by a spectrophotometric enzymatic assay) in leucocytes and erythrocytes as well as the amount of MnSOD in leucocytes (absent in erythrocytes) by western blot. Since the metabolism of H_2O_2 depends on the general condition of the participant (genetics and environmental factors), the levels of these components are stable at the erythroblastic stage of the erythrocyte making these cells suitable for the study of the cumulative factors influencing the metabolism of GSH.

Neighbourhood environment

Participants' residential address postal codes are recorded. Residential neighbourhood environments (defined based on the most relevant buffer zone for the given indicator) are characterised using data available for all postal codes in Canada via the Canadian Urban Environmental Health Research Consortium that facilitates the use of urban environmental exposure data in health research.[83] Neighbourhood environment indicators include: (1) the Canadian Active living Environment index,[84] (2) an indicator of the quantity of green vegetation (Normalized Difference Vegetation Index) and (3) material and social deprivation indices[85] and air quality indicators.

Markers of CVD

The spectrum of early surrogate markers of CVD risk in children and adolescents considered in this project include both novel markers such as cardiac and endothelial structure/function (primary outcomes) and traditional markers, such as hypertension and dyslipidemia (secondary outcomes).

Cardiac structure and function

CMR is the accepted gold standard for quantification of left ventricular (LV) volumes, mass and function[86–88] and is considered uniquely useful for studying myocardial tissue abnormalities in diabetes. We are acquiring short axis and long axis cine images and native myocardial T1 maps, as tissue marker for myocardial fibrosis in diabetes.[86 89] As these techniques are non-invasive, without contrast agents and as CMR does not use any radiation or radioactivity, it is highly suitable for an application in adolescents. Measurements of volumes, mass, as well as diastolic and systolic function are performed based on cine CMR images, using standard parameters (LV End-Systolic Volume Index, LV ejection fraction, LV circumferential and longitudinal strain). CMR images are analysed using software certified for CMR image analysis (cvi, Circle Cardiovascular Imaging, Calgary, Alberta, Canada).

Arterial structure and function

Arterial structure and function is assessed using an iE33 Doppler ultrasound with an 11 MHz linear probe. Arterial stiffness, which reflects the lack of distensibility of the vessel under study, is determined by pulse wave velocity; indices of elasticity and resistance are assessed at the level of the central aorta.[90 91] Endothelial function is determined by flow-mediated dilation of the right brachial artery at rest and in response to post-ischemic hyperemia after distal artery occlusion, as per published guidelines.[92] Flow-mediated dilation studies use exposure of local vasculature to ischemia in order to estimate endothelium-mediated vasodilation (mostly nitric-oxide release).

Hypertension

Repeated measures of blood pressure are obtained using standardised protocols.[93] Age-specific, sex-specific and height-specific percentiles and z-scores for blood pressure are computed using the National High Blood Pressure Education Program (NHBPEP) data.[94]

Dyslipidemia

Total cholesterol, free cholesterol and triglycerides are determined enzymatically by commercial colorimetric kits (Roche Diagnostic, Indianapolis, USA).

Data management

Participants are assigned a unique identifier, which can only be linked to personal data on a secured server accessible by the study investigators. Data from all assessments are entered in an Oracle database by a trained research assistant. All data will be assessed for completeness and plausibility once data entry is completed, and any queries will be resolved by the research coordinator.

Analyses

The distribution of correlates and outcomes will be examined using descriptive statistics and graphs. Objective 1: means and 95% CIs will be used to estimate traditional and novel markers of CVD risk, and comparisons between adolescents with and without diabetes (controls) will be made using multivariable regression analyses, adjusting minimally for age, sex, pubertal stage, ethnicity and family history of CVD. Spearman's rank correlations will be used to assess the correlation between novel and traditional measures of CVD risk in both groups. Objectives 2 and 3: to establish the association between lifestyle behaviours/inflammation/oxidative stress/neighbourhood features

(main exposure variables) and both traditional and novel markers of CVD risk, outcomes and exposures of interest will be analysed as continuous variables. Linear regressions will be estimated and continuous covariates will be investigated for non-linearity. All multivariable models will be minimally adjusted for age, sex, Tanner stage, season (for models including physical activity) and where relevant, duration of diabetes. Meaningful group differences will be formally tested using, among other methods, interaction terms between main exposures of interest and group status (T1D vs healthy control).

Multiple imputation techniques using chained equations will be used to account for missing data.[95] Goodness of fit will be assessed using adjusted R^2, residual and influential analysis. All analyses will be performed in SAS version 9.4.

Power

Using SAS, we have computed the statistical power associated with these analyses for a sample of 200 (ie, 100 subjects per group). For comparisons of means, we expressed their difference in terms of effect sizes. In the absence of previous thresholds, we aimed to detect a conservative effect size of 0.5, deemed clinically significant. With 100 subjects per group, we have over 80% power to detect a 'shift' in means of 0.5 SD between adolescents with T1D and healthy controls. Similarly, we will have over 80% power to detect a partial correlation of at least 0.3 while adjusting for five other covariates with a sample size of 100 per group. Since we also wish to compare associations between groups, we calculated the power to detect an effect modification. If we need n subjects in each category of the modifier to achieve a given power to detect a common correlation Δ_R, we would need 2n subjects in each of these two categories of the modifier to have that same power to detect a difference of R between the two categories. Given that we have power to detect correlations of 0.3 with a sample size of 100, the analysis of 100 subjects with diabetes and 100 healthy subjects yields 80% power to detect an effect modification of 0.6 between both groups. We acknowledge, however, that power will be lower when testing smaller interaction effects.

Data monitoring and harms

An independent data monitoring and safety committee is not involved, as this study is deemed to have a low risk of harm. In case of an adverse event, participants will be referred to the hospital emergency department or their treating physician.

Auditing

For monitoring, control and safety, it is possible that representatives from the Sainte-Justine University Health Center Research Ethics Board or the funding agencies review study files, as well as medical charts. All these individuals and organisations adhere to policies on confidentiality.

Confidentiality and access to data

Only the investigators and authorised members of the research team at CHU Sainte-Justine have access to study data. All data are stored on a secure server, with password-protected access. Data will be deidentified using a personal identifier for all analyses. Electronic records and coded biological specimens (plasma, urine) will be kept as long as the researchers responsible for this biobank will be able to assume its full responsibility.

PATIENT AND PUBLIC INVOLVEMENT

Built around the needs expressed by a large sample of patients with T1D from our clinic in a survey on lifestyle habits and barriers to being active, our project addresses critical gaps related to CVD in youth with T1D. Knowledge users from the diabetes clinic were involved in the protocol development in order to enhance the clinical applicability of our findings. Families are invited to provide feedback on study process, notably regarding the burden of participation. Knowledge users will be involved in the interpretation of findings, and results will be disseminated, among other strategies, via specific patient-led platforms that our research team is involved in (eg, the Virtual Patient Network (VPN) project, http://www.youngdiabetes1.ca/).

ETHICS AND DISSEMINATION

The study was approved by Sainte-Justine University Health Center Research Ethics Board (2016-936). Written informed assent and consent are obtained for each child and a parent, respectively, by a trained research nurse. Any protocol amendments (eg, changes to eligibility criteria, recruitment strategy or study outcomes) will be submitted to the Research Ethics Board for approval.

Data will be published and presented at national and international scientific meetings. MH is a member of the Diabetes Canada Clinical Practice Guidelines expert committee, and is therefore well positioned to share findings with health professionals working in the area of diabetes across Canada, as well as to patients and families. Moreover, several investigators involved in this project are members of the *Network of Research in Cardiometabolic Health, Diabetes and Obesity*, a network active in promoting research and knowledge translation in this field (TAB is the director of KT axis). To reach beyond this group, we will organise popular education events (eg, information sessions within the hospital, scientific cafés) in conjunction with provincial and national pediatric diabetes organisations (eg, Fondation Ressources pour les Enfants Diabétiques—FRED). Findings from this project will inspire innovative interventions to prevent CVD among youth with diabetes. The 'Centre CIRCUIT' of the Sainte-Justine University Health Center (www.centrecircuit.com), of which MH and J-LB are codirectors, is an avant-garde program for the prevention of CVD in at-risk youth, an established infrastructure where such interventions

can then be applied and tested. Finally, several investigators (VD, MH, AVH, J-LB, A-MN, MF, TAB, M-EM, EL) teach through clinical bedside training or within education programs and can communicate findings to both future and current professionals.

Our findings, linking inflammation, oxidative stress, lifestyle habits and environmental factors to the most sensitive methods to detect myocardial and endothelial morphologic/functional changes that herald CVD, will provide critically needed information for the development of effective preventive strategies for youth with T1D.

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Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

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