


Motivational Interview to improve vascular health in Adolescents with poorly controlled type 1 Diabetes (MIAD): a randomized controlled trial

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ABSTRACT

Introduction We studied if motivational interviewing (MI) added to standard educational care (SEC) improves vascular health in adolescents with poorly controlled type 1 diabetes. **Research design and methods** 47 adolescents with type 1 diabetes of at least 2 years duration and hemoglobin A1c >75 mmol/mol (>9.0%) on two visits were randomized to MI+SEC or SEC. We also compared vascular health parameters of patients with type 1 diabetes at trial baseline with a group of healthy historical controls matched for age and body size. **Results** 39 adolescents (20 MI+SEC) completed the vascular health study. At 12 months, parameter changes were not statistically significantly different between MI+SEC and SEC (carotid-femoral pulse wave velocity (cfPWV): mean difference 0.052 m/s (95% CI -0.395 to 0.500, p=0.81); carotid-radial PWV (crPWV): 0.118 m/s (95% to 0.478 to 0.713, p=0.69), carotid intima-media thickness (IMT): 0.002 mm (95% CI -0.37 to 0.40, p=0.93), systolic blood pressure (BP) z-score: 0.495 (95% CI -0.099 to 1.09, p=0.10). At baseline, duration of type 1 diabetes was associated with radial IMT (r=0.430, p=0.007) and cfPWV (r=0.373, p=0.018), and carotid, femoral and brachial IMT were correlated with continuous glucose monitoring (CGM) SD (r=0.440, p=0.017; r=0.377, p=0.048; r=0.387, p=0.038). There was an inverse association between CGM time-in-range (3.9–10.0 mmol/L) and crPWV (r=-0.476, p=0.022) changes. Systolic BP change was associated with body mass index change (r=0.374, p=0.019) and IMT change (r=0.461, p=0.016 for carotid IMT; r=0.498, p=0.010 for femoral IMT). PWVs were higher and common carotid compliance lower among patients with type 1 diabetes at baseline compared with healthy controls, but no other differences were found.

Conclusion There was no effect of MI added to SEC on vascular health parameters. Although disease duration and glycemic control were associated with vascular health at baseline, there were only limited associations between glycemic control and vascular health parameter changes. Vascular health parameter changes were interrelated suggesting clustering of cardiovascular risk.

Trial registration number NCT02637154.

INTRODUCTION

Patients with type 1 diabetes (T1D) with optimal glycemic control suffer less from

Significance of this study

What is already known about this subject?

- Poor glycemic control during adolescence predict overall long-term cardiovascular morbidity in individuals with type 1 diabetes.
- There is a lack of previous randomized controlled intervention trials to improve both glycemic control and vascular health in adolescents with type 1 diabetes.

What are the new findings?

- The trial found no effect of motivational interviewing when added to standard care on adolescent glucose and vascular health parameters during a 12-month follow-up in adolescents with type 1 diabetes.
- Arterial stiffness was increased at baseline in adolescents with type 1 diabetes compared with age-matched and body size-matched healthy adolescents.
- Vascular health parameters improved during follow-up in adolescents with type 1 diabetes with adverse levels at the time of poor glycemic control at baseline.
- Longitudinal vascular health parameter changes were interrelated consistent with clustering of cardiovascular risk in adolescents with type 1 diabetes.

How might these results change the focus of research or clinical practice?

- The study highlights the importance to monitor vascular health, in addition to glycemic control, and to introduce preventive measures focusing on cardiovascular risk among adolescents with type 1 diabetes.

long-term vascular complications than those with poor control. Increased hemoglobin A1c (HbA1c) levels predict these complications. The development of diabetic complications seems to accelerate during puberty, and 5–7 years poor metabolic control during adolescence or young adulthood markedly increases the incidence of microvascular

or macrovascular complications during the following 6–10 years.^{1–6} Optimal adherence to treatment during adolescence in turn has been reported to reduce the risk of microvascular complications, even if the beneficial glucose control is lost later in life, implicating that puberty is an important time period for predicting the overall long-term morbidity in individuals with T1D.^{7–10}

Insulin resistance and impaired metabolic control are common problems in adolescents with T1D despite significant technological advancements including better tools for glycemic control. Treatment during puberty can be complicated and treatment adherence often declines in transition to adolescence.¹¹ At present, there is a lack of evidence based methods for clinicians treating adolescents with poor glycemic control to improve treatment adherence. Some small population-based studies report different interventions including motivational interviewing (MI) provided by clinicians, ‘diabetes trainers’ or psychologists in variable setting and with variable glycemic control outcomes ranging from substantial¹² to no benefit.^{13 14} The clinical utility of MI added to a standard educational care (SEC) setting in the follow-up of adolescents with T1D is still unclear. A number of studies have also addressed associations between glycemic control and different parameters of vascular health in adolescents with T1D in both cross-sectional^{15 16} and longitudinal settings,^{17 18} but we are not aware of a previous randomized controlled intervention trial to improve both glycemic control and vascular health in youth.

Our hypothesis was that MI added to usual SEC would improve glycemic control resulting in better vascular health in adolescents with poorly controlled T1D. Our aim was thus to study the effect of MI on glycemic control and its associations with vascular health parameters in a randomized trial. We also compared adolescent poorly controlled T1D vascular health parameters at trial baseline with a group of healthy controls matched for age and body size.

METHODS

The randomized controlled Motivational Interview in Adolescents with poorly controlled type 1 Diabetes (MIAD) trial with participants allocated to MI+SEC (intervention) integrated to clinicians’ daily practice, as a part of normal clinical visit, or to usual SEC (control) was conducted at the Pediatric Diabetes Units of Helsinki University Hospital (Children’s Hospital and Jorvi Hospital) between October 2015 and August 2018. Inclusion criteria at enrollment were age between 12 and 15.9 years, pubertal (Tanner) stage 2 or more and a diagnosis of T1D with at least 2 years duration and HbA1c >75 mmol/mol (>9.0 %) on two consecutive visits indicating poor glycemic control. Exclusion criteria were celiac disease with poor control, diagnosis of psychiatric disease and other chronic disease requiring systemic glucocorticoid treatment.

Study subjects and protocol

Forty-seven Caucasian subjects (20 females) were recruited and entered the study. All subjects with T1D were attending ordinary government-run Finnish comprehensive schools. Randomization was performed in permuted blocks of six patients with balanced numbers of intervention and control subjects for each treating physician. Five subjects were not eligible for the cardiovascular assessment as they were followed up in another center, one subject randomized to intervention was excluded prior to cardiovascular assessment at baseline due to technical problems, and two subjects, one randomized to control and one to intervention entered the study, but moved to another area and were lost for follow-up. Another 10 subjects, 6 intervention and 4 controls, completed the study, but lack follow-up ultrasound data due to technical problems related to equipment breakdown and missing images. This manuscript reports data of all 39 subjects with T1D (20 MI+SEC) that participated in vascular health assessments. Patients were followed up by the treating physician every 3 months. HbA1c was assessed every 3 months. One subject (intervention) reported regular smoking. Vascular, body composition and additional fasting venous blood sampling were performed at baseline and 12 months. The investigator was blinded to all outcome variable assessments.

In addition to the randomized controlled MIAD study, we compared arterial structure and stiffness parameters of subjects with T1D at baseline with a historical healthy control group (case-control design). The healthy control group is described in online supplementary material. The proportion of females was slightly lower (15/40) compared with proportion of females among randomized patients with T1D (19/41). The historical control vascular health data have been reported previously.¹⁹

Motivational interviewing intervention

Physicians randomized (1:1) to employ MI were trained by a psychologist familiar with the method in a 2-day workshop. Rollnick’s textbook about MI in healthcare was used as a schoolbook for the method.²⁰ Four important principles that form the basis of MI treatment are: (a) expression of empathy, (b) developing discrepancy between status quo and change, (c) rolling with resistance (as a natural phenomenon) and (d) supporting self-efficacy. The MI intervention was applied at each patient visit by incorporating the MI principles to usual SEC discussions, with a focus to improve adherence to glucose follow-up and insulin administration, as well as emphasizing personal benefits of improving glycemic control. SEC material provided to both groups included a test for carb counting and visual material on HbA1c targets, blood glucose targets, long-term diabetes complications, ketoacidosis and hypoglycemia. Differences in subject SEC status or level was not assessed but their skills in carbohydrate counting was assessed with standard visual material by a diabetes nurse at baseline and 12-month study visits.

Blood glucose monitoring

Continuous glucose monitoring (CGM; 6 days blinded continuous glucose monitoring, iPro, Medtronic or patients own CGM (if in use)) was performed at baseline and 12 months in all subjects with T1D. CGM data were available for 11 individuals in the intervention (MI+SEC) and 18 in the control (SEC) group at baseline, and for 14 individuals in the intervention and 16 controls, at 12 months. Both baseline and 12-month CGM recordings were available in 22 patients (9 intervention and 13 controls). Mean sensor glucose level, SD of sensor glucose values calculated coefficient of variation (CV, SD/mean) and time-in-range (TIR; defined as sensor glucose between 3.9 and 10.0 mmol/L) were analyzed from blinded CGM curves to define glycemic control and variability.²¹

Pulse wave velocity

All vascular health measures were obtained and analyzed with the investigator (TS) blinded to patient characteristics and study group. Regional arterial pulse wave velocity (PWV) to assess arterial stiffness was measured using mechanosensors (Complior Analyse, Alam Medical, Saint-Quentin-Fallavier, France) at rest in supine position to simultaneously assess transit times between right carotid, femoral and radial arteries for central or aortic (right carotid-femoral) and peripheral or brachial (right carotid-radial) PWVs. The direct distance between recording sites were measured using a tape measure to the nearest 0.1 cm. The distance from the jugulum to the carotid pulse was subtracted from the direct carotid-radial distance, and the carotid-femoral distance was multiplied by 0.8. Two recordings were obtained with a third recording performed in the setting of a >0.5 m/s (10%) difference between measurements. In the setting of more than two measurements, the results with the lowest tolerance values were used in analyses. The mean of at least two measurements was used in final analyses. The CV for repeat measurements were 3.8% for carotid-femoral PWV and 2.8% for carotid-radial PWV (n=80, including baseline and follow-up assessments). Historical controls were assessed (by TS) during identical conditions and criteria for distance assessments using the SphygmoCor system (AtCor Medical, Itasca, Illinois, USA) to assess transit time. SphygmoCor and Complior Analyse has previously been shown to provide equivalent PWV results and without bias.²²

Vascular ultrasound

Very high-resolution ultrasound images were obtained (TS) with Vevo 770 and, due to breakdown of the equipment beyond repair, with Vevo MD (VisualSonics, Toronto, Canada) for the last 10 baseline assessments and for all but 3 follow-up assessments. The Vevo 770 was equipped with mechanical RMV-710B, RMV-712 and RMV-708 transducers with center frequencies 25, 35 and 55 MHz, respectively. The Vevo MD was equipped with electronic UHF22, UHF48 and UHF70 transducers, with 15, 30 and 50 MHz center frequencies, respectively. Imaging was performed and measurements obtained

as described.²³ Ultrasound methods are described in online supplementary materials. Historical controls were assessed by TS with the Vevo 770 system using identical imaging protocols including transducers, anatomical locations, cardiac cycle and offline measurement criteria.

Anthropometrics and body composition

Subject height was assessed with an electronic stadiometer (Seca & co. kg, Hamburg, Germany) and measured to the nearest 0.1 cm. Weight was assessed using an electronic scale (Seca 770, Seca & co. kg) to the nearest 0.1 kg. Hip and waist circumference were measured with a tape measure to the nearest 0.5 cm. Z-scores for child height and body mass index (BMI) were derived using the recent Finnish reference data.²⁴ Overweight and obesity was defined using International Obesity Task Force (IOTF) criteria.²⁵

Body composition was assessed with dual-energy absorptiometry (DXA, Hologic Discovery A, Waltham, Massachusetts, USA) at 0 and 12 months. For historical controls, lean body mass (LBM) was derived using the previously DXA-based validated formula²⁶ and fat mass was calculated as LBM subtracted from total body weight. Body fat percentage was calculated as fat mass divided by total body weight.

Blood pressure

Blood pressure (BP) was assessed according to US National High Blood Pressure Education Program (NHBPEP) 4th report guidelines using three repeat oscillometric measurements (Dinamap ProCare 200, GE) at rest in sitting position after 15 min rest. A difference of <5 mm Hg between measures was deemed appropriate. The mean of the two lowest readings were used in analyses. Systolic BP and diastolic BP z-scores were generated using the 4th report reference.

Blood work and analyses

HbA1c levels were measured during each visit from fingertip samples (Afinion). All other blood samples were taken by a trained laboratory technician after fasting. Plasma glucose was determined using enzymatic hexokinase assay (Roche Diagnostics, Basel, Switzerland), low-density lipoprotein, high-density lipoprotein, triglycerides and total cholesterol were determined using enzymatic assays (Abbott, Illinois, USA). 1,5-Anhydroglucitol (1,5-AG) was analyzed from serum samples according to assay brochure using a commercial kit (GlycoMark, New York, USA). High-sensitivity C reactive protein (hs-CRP) was determined immunochemically. Microalbuminuria was assessed from spot urine samples by determining albumin-to-creatinine ratio. Urine albumin was determined immunochemically and urine creatinine enzymatically. Microalbuminuria was defined as present when albumin-to-creatinine ratio was >3.5 mg/mmol in spot urine sample.

Data analyses

Data are presented as mean and SD or as count and percentage. All continuous variables were assessed for

normal distributions graphically using histograms as well as with the Shapiro-Wilk test.

Predefined primary outcome of the MIAD study was change in HbA1c and glycemic variability between baseline and 12 months, and glycemic variables were included as background variables to study associations with laboratory measures of cardiovascular risk and vascular health parameters in the present manuscript. Predefined secondary vascular health outcomes were change in arterial IMT, PWV, blood pressure and inflammatory marker hs-CRP between baseline and 12 months. Heart rate, anthropometrics, and body composition parameters were included as confounders in the analyses.

Predefined power calculations for the MIAD were based on the probability of a significant 1% absolute difference between HbA1c change from baseline to 12 months between intervention (MI+SEC) and control (SEC). With an HbA1c SD of 1.24, power of 80% and alpha 0.05, a maximum dropout rate of 8%, a total of 50 patients with T1D would have been needed for the study. Predefined power calculations for the case-control study part were based on the probability of a 10% absolute difference between patients with T1D at baseline and healthy controls. With an IMT SD of 0.07 and PWV SD of 1.0, power of 80% and alpha 0.05, a total of 40 patients with T1D and healthy 40 controls would have been needed for the study.

Associations between variables obtained at baseline were initially analyzed. Patients with T1D were compared with historical controls, and T1D patient z-scores with a healthy reference population mean, using simple Student's t-test. Associations between vascular health parameters and background variables were then explored with bivariate Pearson's correlations including both patients with T1D and historical controls in the analyses. Associations between glycemic variables and vascular health variables were explored similarly among patients with T1D.

Main outcome measures related to intervention were assessed comparing mean differences (and 95% CIs for mean difference) between intervention and control groups at follow-up based on univariate analysis of covariance (General Linear Model (GLM)) models entering treatment as fixed factor and baseline as covariate. Associations between baseline values and absolute change in values between baseline and 12 months, as well as associations between absolute change between glucose and vascular health parameters from baseline to 12 months was explored with scatter plots and Pearson's correlations. Bonferroni corrections were not made and $p < 0.05$ was considered to be statistically significant. Analyses were performed with SPSS Statistics V.25.

RESULTS

Vascular health at baseline and comparison with historical controls

No statistically significant differences between patients with T1D and historical controls or between patients with T1D between MI+SEC and SEC groups were found in sex,

age, body size or body composition (table 1). Central and peripheral PWV were higher and local common carotid compliance was lower among patients with T1D compared with historical controls (table 2). There were no statistically significant difference in arterial wall layer thickness or lumen diameter between patients with T1D and historical controls (table 2). BMI z-score was higher and diastolic BP z-score lower among patients with T1D compared with the reference population (tables 1 and 2).

At baseline, age was positively associated with femoral artery intima-media thickness (IMT) and intima-media-adventitia thickness (IMAT), and LBM positively associated with peripheral artery IMT and IMAT (online supplementary table 1). Systolic BP z-score was associated positively with PWV, local carotid artery compliance and stiffness, as well as with carotid and radial artery IMT. There were no significant associations between different measures of adiposity (BMI z-score, waist-to-hip ratio, body fat percentage) or sex and vascular health parameters (online supplementary table 1). Duration of T1D was positively associated with radial IMT and carotid-femoral PWV (online supplementary table 2, figure 1A), and these associations remained statistically significant when adjusting for age, systolic BP z-score and BMI z-score with multiple linear regression analyses. Carotid, femoral and brachial IMT was correlated with CGM SD (figure 1B), and carotid IMT in addition with CGM CV. No significant associations between BP or PWV, and glycemic control variables were found. Similarly, hs-CRP was correlated with systolic BP z-score (online supplementary table 3). There were no consistent associations between lipids and vascular health parameters (online supplementary table 3).

Change in glucose and vascular health parameters

No statistically significant differences between the MI+SEC and SEC groups were found in HbA1c, 1.5-AG, body size, body composition, blood pressure, arterial structure or stiffness parameters including arterial IMTs and PWVs, fasting blood lipids or hs-CRP levels from baseline to 12 months when adjusting for baseline levels (table 3).

Associations between changes in different parameters of glycemic control including HbA1c, 1.5-AG and CGM recordings (mean glucose levels, SD, CV and TIR), and changes in vascular health parameters (PWVs, IMT, BPs) were found not statistically significant (table 4), except for a statistically significant inverse (negative) association between change in TIR and carotid-radial PWV ($r = -0.476$, $p = 0.022$, figure 1E).

There were significant associations between longitudinal changes in vascular health parameters. Change in systolic BP was correlated with change in BMI ($r = 0.374$, $p = 0.019$, figure 1D) and change in IMT ($r = 0.461$, $p = 0.016$ for carotid IMT; $r = 0.498$, $p = 0.010$ for femoral IMT; figure 1C). Change in hs-CRP was positively associated with diastolic BP change, but not with systolic BP change, and nearly significant trends between change in hs-CRP

Table 1 Characteristics of study subjects at baseline

Variable	T1D intervention	T1D control	T1D all	Historical controls
N	20	21	41	40
Male sex (N)	12 (60%)	10 (48%)	22 (54%)	25 (63%)
Age (years)	14.6 (0.9)	14.6 (0.8)	14.6 (0.8)	14.7 (1.0)
Duration of diabetes (years)	8.1 (3.6)	7.9 (3.8)	8.1 (3.7)	
Continuous subcutaneous insulin infusion	13	14	27	
Insulin multiple daily injections	7	7	14	
Smoking (n)	1 (5%)	0	1 (2%)	0
Height (cm)	167.8 (7.2)	167.4 (6.2)	167.6 (6.6)	165.7 (10)
Weight (kg)	65.1 (12.0)	61.7 (13.4)	63.3 (12.7)	58.6 (13.0)
BMI (kg/m ²)	23.1 (3.7)	22.0 (4.4)	22.5 (4.1)	21.2 (3.5)
BMI z-score	0.76 (0.88)	0.39 (1.02)	0.57 (0.96)***	0.22 (0.91)
Waist (cm)	78.7 (9.3)	74.6 (10.4)	76.6 (10.0)	NA
Waist-to-hip ratio	0.84 (0.06)	0.81 (0.05)	0.83 (0.05)	NA
Waist-to-height ratio	0.47 (0.05)	0.45 (0.06)	0.46 (0.06)	NA
Lean body mass (kg)†	40.7 (7.1)	38.7 (6.1)	39.7 (6.6)	42.5 (8.9)
Fat mass (kg)†	17.7 (7.0)	17.0 (8.9)	17.3 (7.9)	16.2 (5.8)
Body fat (%)†	28.9 (7.8)	28.4 (9.1)	28.6 (8.3)	27.6 (5.3)
Body surface area (m ²)	1.73 (0.18)	1.69 (0.19)	1.71 (0.19)	1.64 (0.22)
Tanner stage				
M2/P3	0	1	1	NA
M4/P3-P4	0	3	3	
M5/P5	8	7	15	
G2P2	0	1	1	
G3P2-P3	5	2	7	
G4P3-P4	5	4	9	
G5P5	1	1	2	
Missing data	1	2	3	
Laboratory data				
HbA1c (mmol/mol)	87.5 (13.7)	84.3 (11.9)	85.9 (12.7)	
HbA1c (%)	10.2 (1.2)	9.9 (1.1)	10.0 (1.2)	
1,5-Anhydroglucitol (µg/mL)	2.16 (1.16)	2.37 (1.16)	2.26 (1.32)	
Continuous glucose monitoring (CGM)‡				
Mean (mmol/L)	12.2 (2.4)	11.4 (2.2)	11.7 (2.3)	
SD (mmol/L)	4.8 (1.3)	5.0 (1.4)	4.9 (1.4)	
CV (%)	39.2 (9.0)	45.1 (13.3)	42.9 (12.1)	
Time-in-range (%)	33 (21)	36 (11)	35 (16)	
Total cholesterol (mmol/L)	4.46 (0.75)	4.83 (1.12)	4.65 (0.96)	
HDL cholesterol (mmol/L)	1.53 (0.35)	1.71 (0.45)	1.62 (0.41)	
LDL cholesterol (mmol/L)	2.77 (0.73)	2.95 (1.00)	2.86 (0.87)	
Triglycerides (mmol/L)	1.15 (0.62)	1.11 (0.99)	1.13 (0.82)	
Alanine aminotransferase (U/L)	14 (5)	20 (14)	17 (11)	
Gamma-glutamyltransferase (U/L)	15 (7)	17 (12)	16 (9)	
hs-CRP (mg/L)	0.54 (0.10–9.64)	0.90 (0.10–11.59)	0.56 (0.10–11.59)	
Microalbuminuria (present)§	2	2	4	

Data are presented as mean (SD) or as count and percentage. hs-CRP is presented as median (range).

***p<0.001 between historical controls and T1D All (and BMI z-score different from population mean for T1D All), other comparisons between historical controls and T1D all as well as T1D controls vs T1D intervention were statistically non-significant (p>0.05).

†Calculated body composition data based on formula is reported for historical controls.²⁶

‡CGM data available for 18 controls with T1D and 11 T1D interventions at baseline. CGM mean is mean glucose, CGM SD is SD of glucose variability, CGM CV is coefficient of variation (SD/mean) and CGM time-in-range is proportion of time glucose between 3.9 and 10.0mmol/L during continuous glucose monitoring.

§Microalbuminuria data at baseline available in 37/41 patients with T1D; microalbuminuria was defined as present when albumin-to-creatinine ratio was >3.5mg/mmol in spot urine. BMI, body mass index; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C reactive protein; LDL, low-density lipoprotein; NA, not assessed; T1D, type 1 diabetes.

Table 2 Vascular health characteristics of study subjects at baseline

Variable	T1D intervention	T1D control	T1D all	Historical controls
N	20	21	41	40
Blood pressure (BP)				
Systolic BP (mm Hg)	114 (10)	115 (10)	115 (10)	NA
Systolic BP z-score	0.17 (0.93)	0.32 (0.89)	0.25 (0.90)	
Diastolic BP (mm Hg)	59 (4)	57 (7)	58 (6)	
Diastolic BP z-score	-0.50 (0.39)	-0.72 (0.61)	-0.61 (0.52) ^{***}	
Pulse wave velocity (PWV)				
Carotid-femoral PWV (m/s)	5.7 (0.9)	5.4 (0.8)	5.6 (0.8) ^{***}	4.0 (0.8)
Carotid-radial PWV (m/s)	7.4 (1.4)	7.2 (0.8)	7.3 (1.2) ^{***}	6.3 (1.1)
Common carotid artery				
Intima-media thickness (mm)	0.41 (0.05)	0.41 (0.04)	0.41 (0.04)	0.42 (0.06)
Lumen diameter (mm)	5.23 (0.38)	5.09 (0.37)	5.16 (0.38) [*]	5.39 (0.46)
Compliance (%/10mm Hg)	2.38 (0.49)	2.51 (0.38)	2.45 (0.43) ^{***}	3.30 (0.76)
Stiffness (no unit)	4.58 (1.02)	4.24 (0.70)	4.40 (0.87)	4.21 (1.09)
Radial artery				
Intima-media thickness (mm)	0.14 (0.02)	0.14 (0.03)	0.14 (0.02)	0.14 (0.02)
Intima-media-adventitia thickness (mm)	0.21 (0.03)	0.21 (0.04)	0.21 (0.03)	0.22 (0.03)
Lumen diameter (mm)	1.76 (0.31)	1.64 (0.23)	1.70 (0.28)	1.78 (0.30)
Brachial artery				
Intima-media thickness (mm)	0.14 (0.02)	0.14 (0.02)	0.14 (0.02)	0.13 (0.02)
Intima-media-adventitia thickness (mm)	0.25 (0.04)	0.26 (0.05)	0.26 (0.04)	0.24 (0.04)
Lumen diameter (mm)	2.98 (0.47)	3.00 (0.32)	2.99 (0.39)	2.98 (0.54)
Femoral artery				
Intima-media thickness (mm)	0.24 (0.04)	0.26 (0.06)	0.25 (0.05)	0.26 (0.05)
Intima-media-adventitia thickness (mm)	0.46 (0.07)	0.50 (0.08)	0.48 (0.08)	0.49 (0.08)
Lumen diameter (mm)	6.23 (0.68)	6.26 (0.74)	6.24 (0.70)	6.69 (1.13)

Data are presented as mean (SD) or as count.

* $P < 0.05$, *** $p < 0.001$ between T1D all and historical controls, other comparisons between historical controls and T1D all as well as between T1D intervention vs T1D control were statistically non-significant ($p > 0.05$).

NA, not assessed; T1D, type 1 diabetes.

and change carotid-femoral PWV and carotid-radial PWV was also observed (table 4). There was a negative correlation between systolic BP at baseline and change ($r = -0.452$, $p = 0.004$, online supplementary figure 1). There was a similar correlation between PWV at baseline and change ($r = -0.685$, $p < 0.001$ for carotid-femoral PWV; $r = -0.765$, $p < 0.001$ for carotid-radial PWV, online supplementary figure 2).

DISCUSSION

This MIAD study was unable to demonstrate a beneficial effect of MI, when added to SEC in the outpatient clinic, on vascular health. Longitudinal changes in vascular health parameters including measures of adiposity (BMI z-score), BP, arterial wall layer thickness (IMT) and stiffness (PWV) were interrelated in the study and consistent with longitudinal clustering of adverse vascular health parameters in the adolescent population with T1D.

Duration of T1D and different measures of glycemic control were positively associated with arterial layer thickness and central aortic PWV at baseline. However, longitudinal changes in measures of glycemic control were not consistently associated with changes in vascular health parameters apart from an isolated finding of a negative association between TIR and peripheral vascular stiffness (carotid-radial PWV). Improvements in vascular health parameters were, nevertheless, seen among patients with T1D with adverse levels at the time of poor glycemic control at study enrollment.

The larger randomized controlled Flexible Lifestyles Empowering Change (FLEX) study reported, similar to our study, no effect of a modified MI intervention compared with usual care only on HbA1c at 18 months among adolescent with T1D.²⁷ Furthermore, this study found no effect of MI on 1.5-AG—a short term biomarker of glycemic variability and excursions.²⁸ The

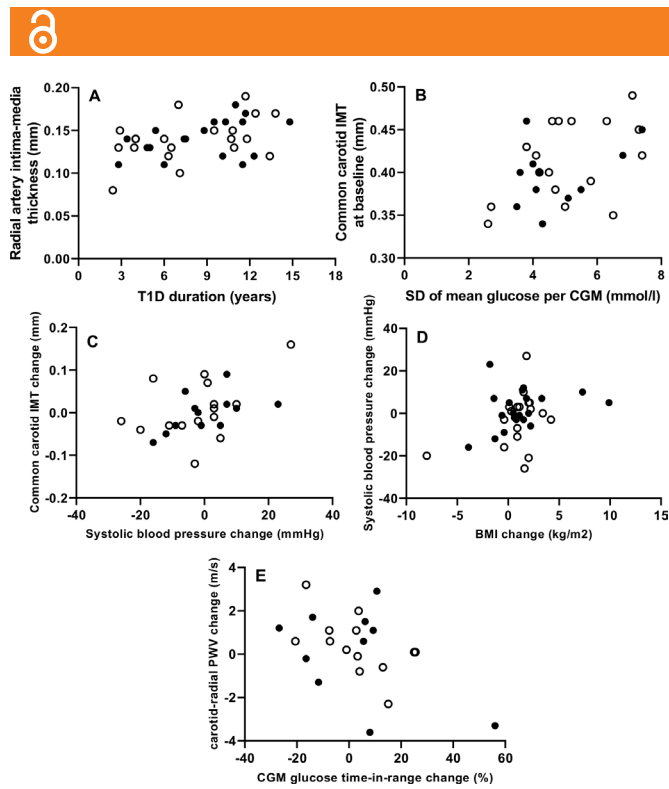


Figure 1 Type 1 diabetes (T1D) duration associated with radial artery intima-media thickness (IMT) at baseline (A), SD of mean glucose per continuous glucose monitoring (CGM) associated with common carotid artery IMT at baseline (B), systolic blood pressure change associated with common carotid artery IMT change (C), body mass index (BMI) change positively associated with systolic blood pressure change (D), glucose time-in-range (TIR) change per CGM change negatively associated with carotid-radial pulse wave velocity (PWV) change (E). Closed circles denote T1D intervention and open circles denote T1D controls.

main MIAD study outcome variable, change in HbA1c as well as changes in CGM will be presented in more detail in another manuscript (Tuomaala *et al*, unpublished data 2020). Presuming a positive association between glycemic control and vascular health parameters, it is not surprising that we were unable to demonstrate a statistically significant difference between SEC and MI+SEC groups in vascular health parameters in the present MIAD study. Although the MI intervention was developed >30 years ago, still the evidence of its benefits in adolescent populations seems somewhat limited.²⁹ On the other hand, 12 months is a relatively short time period to assess the effect of MI on long-term glycemic control and vascular health as change in subject's behavior and vascular health may take much longer, especially when assessing arterial wall structures among adolescents with T1D.³⁰

We were unable to find a randomized controlled trial addressing the potential effect of MI, educational or psychosocial program on vascular health in adolescent patients with T1D with poor glycemic control. Previous cross-sectional and longitudinal studies show increased PWV among patients with T1D compared with healthy controls,¹⁶ interrelations between diabetes duration and IMT,³¹ as well as increasing BMI z-score and progression

of carotid IMT,^{18 32} and increase of BP with age and progression of PWV.¹⁷ We found no difference in arterial IMTs between patients with T1D and healthy controls, which is in line with earlier studies reporting differences confined to the carotid bulb IMT only but not in other carotid artery segments.³³ Presence, clustering and worsening of CV risk factors have been found to be associated with an increased central PWV among adolescent patients with T1D.³⁴ Furthermore, previous Swedish registry data show that coronary artery disease is nine times more common among patients diagnosed with T1D early in life compared with age-matched controls.³⁵ The adverse effects of longitudinal cumulative cardiovascular risk exposure from adolescence to adulthood on vascular health is well established in non-diabetic populations.³⁶ Our results support these previous findings, although we were unable to confirm associations between declining glucose control and increased central PWV. However, Gordin *et al* showed an acute increase in right arm arterial stiffness, but not in central aortic arterial stiffness, during an acute hyperglycemia clamp study among males aged 18–40 years with T1D and relatively good glycemic control (HbA1c 7.9%±0.9%).³⁷ Our results showing an association between an improvement in CGM TIR and a decrease in right arm PWV is in line with this and suggests that peripheral arterial stiffness might be more sensitive to excessive or unstable blood glucose variations compared with central aortic stiffness.

This study is limited due to a small sample size and short follow-up. The study inclusion criteria of poor glycemic control was simple and did not include in-depth motivational or other psychological nor diabetes self-management profiling. In addition, the intervention was focused on improving glycemic control, and did not directly address cardiovascular risk or vascular health. Although retention of patients with T1D was good, we still acknowledge some missing ultrasound imaging and CGM data. Measures of vascular stiffness (PWV) were, however, complete and we were able to include a historical healthy control group matched for age and body size as well. Endothelial function assessments using flow-mediated dilatation (FMD) or peripheral reactive hyperemia (EndoPat) were not feasible due to known high technical measurement variance in longitudinal study settings encompassing several months requiring large sample sizes for adequate study power.^{38 39} We, however, included a representative sample and applied recently validated novel biomicroscopy technology including multiple arterial site assessments and providing more detailed information regarding the arterial wall structure.

In conclusion, we observed no statistically significant benefit of MI, when added to SEC, on vascular health among adolescents with T1D with poor glycemic control. Although we found significant associations between T1D duration, glycemic control and vascular health parameters at baseline, we were able to see only limited associations between changes in glycemic control and changes in vascular health parameters during follow-up. Adverse

Table 3 Absolute change from baseline to 12-month follow-up, mean difference and CIs of mean difference for anthropometric, laboratory and vascular outcomes of the intervention and control groups

Variable	T1D intervention change	T1D control change	Mean difference	95% CI	P value
N	19	20			
Height (cm)	1.8 (6.8)	5.5 (6.3)	-3.66	-7.592 to 0.273	0.067
Weight (kg)	4.9 (7.7)	6.6 (8.1)	-1.18	-6.206 to 3.838	0.635
BMI (kg/m ²)	1.2 (3.0)	0.9 (2.4)	0.55	-1.179 to 2.289	0.520
BMI z-score	0.13 (0.73)	0.12 (0.64)	0.10	-0.32 to 0.53	0.633
Waist (cm)	3.3 (10.7)	2.6 (6.7)	2.26	-3.365 to 7.896	0.420
Waist-to-hip ratio	0.01 (0.13)	-0.01 (0.04)	0.055	-0.006 to 0.116	0.078
Waist-to-height ratio	0.01 (0.07)	0.006 (0.04)	0.025	-0.010 to 0.059	0.156
Lean body mass (kg)	2.6 (5.8)	5.4 (5.2)	-2.6	-6.18 to 1.04	0.157
Fat mass (kg)	1.8 (3.2)	1.6 (1.4)	0.23	-1.41 to 1.87	0.776
Body fat (%)	0.016 (0.025)	0.013 (0.012)	0	-0.13 to 0.13	0.994
HbA1c (mmol/mol)	-3.5 (16.8)	0.9 (18.8)	-1.1	-10.8 to 8.5	0.817
HbA1c (%)	-0.34 (1.51)	0.07 (1.73)	-0.12	-1.00 to 0.76	0.792
1,5-Anhydroglucitol (µg/mL)	0.23 (1.50)	-0.37 (1.47)	0.38	-0.46 to 1.22	0.360
Total cholesterol (mmol/L)	-0.04 (0.66)	-0.36 (0.87)	0.12	-0.38 to 0.62	0.635
HDL cholesterol (mmol/L)	-0.14 (0.23)	-0.31 (0.28)	0.09	-0.06 to 0.24	0.227
LDL cholesterol (mmol/L)	0.02 (0.60)	-0.25 (0.71)	0.12	0.28 to 0.53	0.549
Triglycerides (mmol/L)	0.29 (0.90)	0.33 (0.86)	-0.04	-0.65 to 0.57	0.896
hs-CRP (mg/L)	0.47 (2.29)	1.33 (2.34)	-0.85	-2.41 to 0.71	0.273
Systolic BP (mm Hg)	1.7 (9.1)	-2.6 (12.3)	3.76	-2.433 to 9.963	0.226
Systolic BP z-score	0.003 (0.88)	-0.572 (1.25)	0.495	-0.099 to 1.09	0.100
Diastolic BP (mm Hg)	-0.4 (5.6)	0.2 (6.2)	1.35	-2.188 to 4.892	0.444
Diastolic BP z-score	-0.100	-0.136	0.203	-0.117 to 0.523	0.207
Pulse pressure	2.1 (7.9)	-2.7 (12.0)	2.34	-3.368 to 8.058	0.411
Carotid-femoral PWV (m/s)	0.11 (1.00)	0.32 (0.83)	0.052	-0.395 to 0.500	0.813
Carotid-radial PWV (m/s)	0.28 (1.66)	0.44 (1.12)	0.118	-0.478 to 0.713	0.691
Common carotid artery					
Intima-media thickness (mm)	-0.008 (0.044)	0.008 (0.069)	0.002	-0.37 to 0.40	0.933
Lumen diameter (mm)	0.082 (0.386)	-0.123 (0.374)	0.227	-0.38 to 0.492	0.090
Compliance (%/10 mm Hg)	0.46 (0.61)	0.44 (0.52)	-0.031	-0.41 to 0.35	0.867
Stiffness (no unit)	0.48 (1.32)	0.62 (0.82)	-0.069	-0.79 to 0.65	0.846
Radial artery					
Intima-media thickness (mm)	-0.011 (0.032)	0.005 (0.020)	-0.013	-0.033 to 0.006	0.158
intima-media-adventitia thickness (mm)	-0.014 (0.038)	0.009 (0.026)	-0.020	-0.43 to 0.004	0.093
Lumen diameter (mm)	0.195 (0.384)	0.069 (0.200)	0.142	-0.054 to 0.339	0.148
Brachial artery					
Intima-media thickness (mm)	-0.008 (0.027)	-0.001 (0.023)	-0.002	-0.018 to 0.014	0.815
intima-media-adventitia thickness (mm)	-0.014 (0.037)	0.008 (0.044)	-0.014	-0.035 to 0.006	0.159
Lumen diameter (mm)	0.170 (0.272)	-0.037 (0.437)	0.207	-0.071 to 0.485	0.137
Femoral artery					
Intima-media thickness (mm)	0.031 (0.082)	0.015 (0.038)	0.012	-0.035 to 0.059	0.590
Intima-media-adventitia thickness (mm)	0.054 (0.159)	0.038 (0.067)	0.004	-0.073 to 0.082	0.905
Lumen diameter (mm)	0.207 (0.263)	-0.128 (0.845)	0.330	-0.275 to 0.935	0.267

Mean differences between intervention and control group at follow-up based on univariate analysis of covariance (GLM) models are adjusted for baseline values. No statistically significant effect of intervention on anthropometrics, body composition or cardiovascular parameters was found. BMI, body mass index; BP, blood pressure; GLM, General Linear Model; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C reactive protein; LDL, low-density lipoprotein; PWV, pulse wave velocity; T1D, type 1 diabetes.

Table 4 Univariate Pearson's correlations between absolute change in glycemic variables and inflammation markers, and vascular health variables between baseline and 12 months

Variable	HbA1c	1.5-AG	Glucose mean	Glucose SD	Glucose CV	Glucose TIR	hs-CRP
Carotid-femoral PWV	0.032	-0.235	-0.132	0.080	0.155	-0.323	0.361 (p=0.061)
Carotid-radial PWV	0.117	0.096	0.066	-0.015	0.026	-0.476* (p=0.022)	0.314 (p=0.062)
Carotid IMT	0.007	0.390	-0.138	0.279	0.335	0.189	-0.193
Carotid compliance	-0.199	0.178	-0.359	0.020	0.061	0.267	0.099
Carotid stiffness	0.131	-0.252	0.318	0.112	0.025	-0.109	-0.140
Femoral IMT	-0.282	-0.103	-0.083	0.094	0.105	0.171	-0.095
Systolic BP	-0.184	0.201	0.001	-0.253	-0.148	-0.009	0.139
Diastolic BP	0.184	0.157	-0.137	-0.100	0.038	-0.263	0.391* (p=0.020)
Pulse pressure	-0.286	0.124	0.065	-0.168	-0.158	0.168	-0.368* (p=0.029)

CGM absolute change data available for 22 patients with T1D (9 intervention and 13 controls), glucose mean is mean glucose during CGM, glucose SD is SD of glucose variability during CGM, glucose CV is coefficient of variation (SD/mean) during CGM and glucose TIR is proportion of time glucose between 3.9 and 10.0 mmol/L during CGM.

*P<0.05.

1.5-AG, 1.5-anhydroglucitol; BP, blood pressure; CGM, continuous glucose monitoring; HbA1c, hemoglobin A1c; hs-CRP, high-sensitivity C reactive protein; IMT, intima-media thickness; PWV, pulse wave velocity; T1D, type 1 diabetes; TIR, time-in-range.

longitudinal changes in vascular health parameters were, however, interrelated suggesting clustering of cardiovascular risk. The study highlights the importance to monitor vascular health, in addition to glycemic control, and to introduce preventive measures focusing on cardiovascular risk among adolescents with T1D in the outpatient clinic.

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