Published in final edited form as:

J Diabetes Complications. 2014 ; 28(6): 762–766. doi:10.1016/j.jdiacomp.2014.06.017.

ABC goal achievement predicts microvascular but not macrovascular complications over 6-years in adults with type 1 diabetes: the Coronary Artery Calcification in Type 1 Diabetes Study

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Abstract

Hypothesis—Vascular complications of type 1 diabetes are thought to cluster. We examined the prevalence and incidence of vascular complications and American Diabetes Association’s ABC goal achievements in a prospective cohort of adults with type 1 diabetes. We hypothesized that ABC achievement at baseline would predict both micro- and macrovascular complications over 6-years.

Methods—Participants (N=652) were 19–56 year old at baseline and re-examined 6-years later. Microvascular complications included diabetic nephropathy (DN), defined as incident albuminuria (AER 20µg/min) or rapid GFR decline (>3.3%/year) by CKD-EPI cystatin C and proliferative diabetic retinopathy (PDR), defined as laser eye-therapy. Macrovascular complications were defined as coronary artery calcium progression (CACp), measured by electron-beam computed-tomography. ABC goals were defined as HbA1c<7.0%, BP<130/80 mmHg, LDL-C<100mg/dL.

Results—ABC control was suboptimal with only 6% meeting all goals. Meeting no ABC goals at baseline compared to meeting all goals was associated with increased odds of developing

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Author Contributions

PB researched, wrote, contributed to discussion, and reviewed/edited the manuscript; DMM researched, contributed to discussion, and reviewed/edited the manuscript; MR designed the CACTI Study, researched, contributed to the discussion and reviewed/edited the manuscript; RJJ contributed to the discussion and reviewed/edited the manuscript; JKSB researched, contributed to the discussion, reviewed/edited the manuscript.

Duality of interest

Drs. Bjornstad, Snell-Bergeon, Johnson and Maahs have no conflict of interest to disclose.

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microvascular complications (OR: 8.5, 2.3–31.5, $p=0.001$), but did not reach significance for CACp (OR: 1.7, 0.8–3.9, $p=0.19$).

Conclusion—ABC achievement at baseline strongly predicted microvascular but not macrovascular complications over 6-years in adults with type 1 diabetes, suggesting a need for novel therapeutic targets to complement conventional risk factors in treating macrovascular complications.

Keywords

type 1 diabetes; microvascular complications; macrovascular complications

Introduction

The incidence of type 1 diabetes is increasing [1, 2], and the economic burden, morbidity and premature mortality affecting the 1.5 million people in the US with this disease is largely due to its vascular complications [3, 4]. Complications of type 1 diabetes occur in both the macro- (e.g. coronary artery disease [CAD]) and microvasculature (e.g. proliferative diabetic retinopathy (PDR) and diabetic nephropathy (DN)) [5]. CAD and DN are the major causes of morbidity and mortality in patients with type 1 diabetes [4, 6]. Micro- and macrovascular complications tend to cluster in subjects with type 1 diabetes [7–9].

Despite significant improvement of hypertension and glycemic control during the past two decades, recent data from NHANES showed that only 18.8% of subjects with type 1 and 2 diabetes achieved all three of the American Diabetes Association (ADA)'s ABC goals (A; HbA1c <7.0%, B; BP <130/80 mm Hg, C; LDL-C <100mg/dL) [3]. Suboptimal ABC control may be due to unattainable goals with current treatment regimens. Moreover, improved hypertension and glycemic control lowers, but does not abolish the risk of vascular complications [10, 11].

The Coronary Artery Calcification in Type 1 diabetes (CACTI) cohort provided the opportunity to determine the prevalence of microvascular (PDR and DN) and macrovascular complications (progression of coronary artery calcification (CACp)) over 6-years in adults with type 1 diabetes. It also allowed us to determine the prevalence of adults with type 1 diabetes who achieved ADA's ABC goals, and explore the associations between ABC control and vascular complications. We hypothesized that ABC goal achievement at baseline would predict the development of micro- and macrovascular complications over 6-years.

Materials and Methods

The CACTI Study enrolled 1416 subjects 19–56 years old, 652 with type 1 diabetes and 764 without diabetes, who were asymptomatic for cardiovascular disease (CVD) at the baseline visit in 2000–02 and then were re-examined 3 and 6 years later, as previously described [12]. Only the 652 participants with type 1 diabetes were included in this analysis. The study

was approved by the Colorado Multiple Institutional Review Board and all participants provided informed consent.

We measured height and weight, and calculated BMI in kg/m². Resting systolic (SBP) and fifth-phase diastolic blood pressure (DBP) (i.e. the silence as the cuff pressure drops below the DBP) were measured three times while the patient was seated, and the second and third measurements were averaged. After an overnight fast, blood was collected, centrifuged, and separated. Plasma was stored at 4 C until assayed. The results were reported in milligrams per deciliter. Total plasma cholesterol and triglyceride levels were measured using standard enzymatic methods, HDL cholesterol (HDL-C) was separated using dextran sulfate and LDL cholesterol (LDL-C) was calculated using the Friedewald formula. High performance liquid chromatography was used to measure HbA1c (HPLC, BioRad variant).

Diabetic nephropathy

We defined DN as incident albuminuria or rapid GFR decline. Albuminuria was defined as microalbuminuria or greater; albumin excretion rate (AER) ≥ 20 μ g/min if timed urine samples were obtained or albumin/creatinine ratio (ACR) ≥ 30 mg/g for spot samples (if timed urine samples were not available). Two timed overnight urine samples were collected and urine creatinine and albumin were measured (RIA, Diagnostic Products) and averaged. At both visits, urinary albumin excretion rate (AER) and albumin/creatinine ratio (ACR) were calculated. Incident albuminuria was defined as the development of albuminuria at the 6-year follow-up in those without albuminuria at baseline. Of the 27 subjects who developed incident albuminuria all had AER calculated, and all but two (n=326/328) of those who did not develop incident albuminuria had AER calculated. Estimated GFR (mL/min/1.73m²) was determined using the CKD-EPI cystatin C equation [13]. There is no standard cutoff for rapid GFR decline, but we employed annual GFR loss $> 3.3\%$ to define rapid GFR decline which has been used by the Joslin Kidney Study, a study population similar to CACTI [14]. Cystatin C was measured in the University of Colorado Hospital clinical lab using the commercially available Dade-Behring assay following package insert instructions on a BNII or Prospec instrument as previously described in detail [15].

Coronary artery calcification

CAC measurements were obtained in duplicate using an ultrafast Imatron C-150XLP electron beam computed tomography scanner (Imatron, San Francisco, CA). The average of the two scores was used as the CAC score for that visit. Scans were repeated on follow-up, an average of 6.1 years after the baseline exam. Progression of CAC was defined as an increase in volume of CAC of ≥ 2.5 square root transformed units. Both subjects with CAC 0 (incident CAC) and positive score (CAC+) at baseline were included in the analyses. This definition of progression has previously been shown to represent significant progression of atherosclerosis [11, 16].

Proliferative diabetic retinopathy

Diagnosis of PDR was based on self-reported history of proliferative retinopathy with laser eye treatment. Self-reported prior laser treatment has been validated as both a sensitive and specific tool for determining PDR [17, 18].

ABC control

ADA's ABC goals are defined as (A; HbA1c <7.0%, B; BP <130/80 mm Hg, C; LDL-C <100mg/dL) [3]. Anti-hypertension medication use was determined by a medication inventory as previously described [12] and all anti-hypertension medications (including beta-blockers, calcium channel blockers, diuretics, ACE inhibitor (ACEi) and/or angiotensin receptor blockers (ARB) were combined for these analyses.

Statistical Analysis

Analyses were performed in SAS (version 9.3 for Windows; SAS Institute, Cary, NC). Differences between ABC goal achievements were assessed using ANOVA for continuous variables and Chi-Squared for categorical variables. Differences between CAC progressors and non-progressors were assessed using Chi-Square for categorical variables, *t*-test for continuous parametric variables and Wilcoxon signed rank-test for continuous non-parametric variables. Incident albuminuria (n=27), incident PDR (n=35) and rapid GFR decline (n=52) were examined separately and together as microvascular complications (n=99, as 15 subjects experienced more than one microvascular complication).

Logistic regression models were employed to determine if CAC at baseline was associated with development of incident albuminuria, incident PDR and rapid GFR decline and CACp. For that reason, we excluded subjects with albuminuria and PDR at baseline in the respective analyses with incident albuminuria and PDR as the outcomes. For rapid GFR decline and CACp, however, we examined progression and therefore did not exclude baseline disease. The following variables were considered for inclusion in these models: age, sex, diabetes duration, BMI, HDL-C, LDL-C, HbA1c, SBP, DBP, antihypertensive medications, statins and smoking status. Logistic regression models were also used to examine the association between ABC goal achievement at baseline with the development of microvascular complications and CACp. The following variables were considered for inclusion in these models: age, sex, diabetes duration, BMI, antihypertensive medications, statins, smoking status and baseline CAC. Significance was based on an α -level of 0.05.

Results

At baseline, 49% of men and 28% of women had detectable CAC ($p < 0.0001$), 27% of men and 17% of women had evidence of albuminuria ($p = 0.005$), and 27% of men and 19% of women reported PDR ($p = 0.02$). Baseline subject characteristics stratified by ABC goal achievements are shown in Table 1. More women met all goals and some goals, and those that met all goals had significantly lower BMI and waist circumference (Table 1).

Over 6-years 9.6% of men and 6.1% of women developed incident albuminuria ($p = 0.22$), 11% of men and 10% of women developed rapid GFR decline ($p = 0.92$), 11.3% of men and 6.0% of women developed PDR ($p = 0.05$) and 52.5% of men and 34.0% of women experienced CACp ($p < 0.0001$). Incidence of vascular complications stratified by ABC goal achievement at baseline is shown in Figure 1.

Microvascular complications are associated with macrovascular complications and vice versa

When considering the relationship between CAC at baseline and incident albuminuria, rapid GFR decline and incident PDR; any CAC at baseline was associated with increased odds of developing albuminuria (OR: 1.6, 95% CI: 1.0 – 2.5, $p=0.04$) and PDR (OR 1.6, 95% CI: 1.0 – 2.5, $p=0.04$) after adjusting for sex, age, diabetes duration and HbA1c. In contrast, the presence of CAC at baseline was not associated with rapid GFR decline by eGFR_{CR} (p=0.62).

When considering the relationship between baseline microvascular complications and CACp; albuminuria at baseline (OR 6.0, 95% CI: 3.1 – 11.9, $p < 0.0001$) was significantly associated with increased odds of developing CACp after adjusting for baseline CAC, age, sex, diabetes duration and HbA1c. Moreover, the associations remained significant after further adjustments for BMI, LDL-C, HDL-C SBP, DBP, antihypertensive medications, statins and smoking (OR 5.1, 95% CI: 2.4 – 10.8, $p < 0.0001$). Rapid GFR decline was also significantly associated with increased odds of developing CACp after adjusting for baseline CAC, age, sex, diabetes duration and HbA1c (OR 2.2, 95% CI 1.0 – 4.9, $p=0.04$). In contrast, PDR (OR 1.5, 95% CI: 0.8–2.8, $p = 0.23$) did not predict CACp in fully adjusted models.

ABC compliance and vascular complications

Thirty-nine subjects met all goals (6%), 478 met some goals (74%) and 127 met no goals (20%). More women than men met all goals (8.8% vs. 2.7%, $p<0.0001$), and more men than women met no goals (26.6% vs. 14.0%, $p<0.0001$). Microvascular complications developed in 8.7% of subjects who achieved all goals, 19.2% who achieved some goals and 49.1% who achieved no goals ($p<0.0001$, Figure 2). In contrast, CACp occurred in 39% of those who met all goals, 40% of those who met some goals and 53% of those who met no goals ($p=0.10$, Figure 2).

Achieving no ABC goals compared to achieving all goals at baseline was associated with increased odds of developing microvascular complications over 6-years (OR: 8.5, 2.3–31.5, $p=0.001$, Table 2). The association remained significant after adjusting for age, sex, diabetes duration, antihypertensive medications, statins, smoking, BMI (OR: 6.5, 1.6–26.3, $p=0.009$). In contrast, achieving no ABC goals compared to achieving all goals at baseline was not significantly associated with CACp over 6-years (OR: 1.7, 0.8–3.9, $p=0.19$, Table 2).

Achieving no goals compared to some goals at baseline predicted CACp (OR: 1.7, 1.0–2.7, $p=0.04$), but adjusting for age, sex, diabetes duration, antihypertensive medications, statins, smoking, BMI and baseline CAC attenuated the association ($p=0.21$).

Discussion

We report baseline prevalence and incidence over 6-years of micro- and macrovascular complications in a contemporary cohort of adults with type 1 diabetes with suboptimal ABC control. Micro- and macrovascular complications had a tendency to cluster in our cohort with strong reciprocal relationships observed between DN and subclinical atherosclerosis.

Achievement of ABC goals strongly predicted microvascular but not macrovascular complications over 6-years supporting the need for novel therapeutic targets to complement ABC control in treating macrovascular complications.

The ADA recommends that most adults with both type 1 and 2 diabetes should achieve a HbA1C <7.0% (<53 mmol/mol), BP <130/80 mm Hg, and LDL-C <100 mg/dL [19]. Data from NHANES [3] suggested that 81.2% of adults with both type 1 and 2 diabetes did not achieve all three ABC goals, which is comparable to the 94% reported in our cohort. Moreover, Alman et al. recently demonstrated that not a single subject with type 1 diabetes in CACTI met the American Heart Association's 7 metrics for ideal cardiovascular health (ICH) [20]. The suboptimal ABC and ICH control may be reflective of unattainable goals for subjects with type 1 diabetes or the lack of sufficiently effective strategies to achieve the goals [21]. Furthermore, although there is robust evidence showing the benefits of ABC and ICH control in reducing vascular complications in type 1 diabetes [3, 20], optimal control does not abolish the risk for complications. For these reasons there is a call for novel therapeutic targets to supplement conventional therapies.

Incidence and prevalence of vascular complications in the present cohort are comparable to what has been reported in other studies when taking into account the studies' time to follow-up [22, 23]. An important finding in our study is the strong association between DN and macrovascular complications. Emerging data suggest that microvascular disease can lead to dysfunction and ischemia of the macrovasculature [24]. Several studies have demonstrated relationships between cardiac biomarkers and microvascular complications in type 2 diabetes [25–27]. Similarly, prospective studies have demonstrated that markers of microvascular disease, such as microalbuminuria, decreased eGFR or retinal vascular abnormalities, are associated with an increased risk of macrovascular events [7, 9, 28–30]. In CACTI, PDR did not independently predict CACp over 6-years. This stands in contrast to what has been reported by Cardiovascular Health Study [8], but is consistent with the findings of EURODIAB [9], where PDR failed to independently predict fatal and nonfatal CVD in fully adjusted models in subjects with type 1 diabetes.

Our data support the need for novel therapeutic targets to complement ABC control in treating macrovascular complications in adults with type 1 diabetes. We have previously shown that both serum uric acid [31] and insulin sensitivity [32–34] are important and potentially modifiable risk factors for macrovascular complications in type 1 diabetes. Moreover, we have published data demonstrating very weak associations between serum uric acid and insulin sensitivity in type 1 diabetes, supporting their independence as risk factors and possibly therapeutic targets [35]. Another important finding of this paper is the strong association between DN and subclinical atherosclerosis which may refine risk stratification for CACp, and enable development of new therapeutic strategies. There is growing evidence that fibroblast growth factor 23 (FGF23) and Klotho factor are mediators of coronary artery calcification in the setting of nephropathy [36, 37], but it remains uncertain whether regulation of these factors will prevent or delay development of macrovascular disease.

There are limitations of this study worth mentioning. First, PDR was self-reported and could have been affected by poor recall, but self-reporting of PDR has recently been validated for subjects with type 1 diabetes with sensitivity and specificity greater than 90% [17, 18]. Moreover, we did not have data on diabetic neuropathy, another important microvascular complication in type 1 diabetes. The use of CAC as a marker of CAD rather than traditional end points such as coronary artery stenosis, myocardial infarction, or death is another important limitation of this study. However, CAC is accepted as a quantifiable, reliable, noninvasive marker of the extent of coronary atherosclerosis, and CACp progression predicts both fatal and nonfatal coronary events [38]. Although we adjusted for a variety of important confounding variables, we cannot rule out the presence of unknown risk factors that may have biased or confounded the present analyses. Results from this study may not be generalizable to significantly younger or older subjects with type 1 diabetes or to cohorts with optimal ABC control, however our data on ABC control is comparable to what was recently published by NHANES [3]. We also acknowledge that microalbuminuria as a proxy for DN is not without controversy [39], and for that reason added rapid GFR decline by cystatin C as a renal outcome, which is a strength of our study.

In summary, micro- and macrovascular complications clustered in our cohort of adults with type 1 diabetes. Especially the presence of DN was strongly associated with increased odds of progression of subclinical atherosclerosis, independent of glycemic control, dyslipidemia and hypertension. ABC goal achievement at baseline strongly predicted microvascular complications, but not progression of subclinical atherosclerosis. We must create better strategies to overcome current barriers to optimal ABC control and also identify novel therapeutic targets to supplement conventional risk factors so individuals with diabetes can live longer and healthier lives without debilitating vascular complications.

Acknowledgments

Support for this study was provided by NHLBI grant R01 HL61753, HL79611, and HL113029, JDRF grant 17-2013-313, and DERC Clinical Investigation Core P30 DK57516. The study was performed at the Adult CTRC at UCD support by NIH-M01-RR00051, at the Barbara Davis Center for Childhood Diabetes and at Colorado Heart Imaging Center in Denver, CO. Dr. Maahs was supported by a grant from NIDDK (DK075360), Dr. Snell-Bergeon by an American Diabetes Association Junior Faculty Award (1-10-JF-50) and Career Development Award (7-13-CD-10). Drs. Petter Bjornstad and Janet K. Snell-Bergeon are guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Figure 1. Incidence of Microvascular Complications over Six years of Follow-up Stratified by ABC Goal Achievement

P=0.052 for albuminuria, P=0.02 for rapid GFR decline, and P=0.003 for PDR

Figure 2. Incidence of macro- and microvascular complications by ABC goal achievement
P = 0.10 for CAC progression and P<0.0001 for microvascular complications

Table 1

Baseline Subject Characteristics Stratified by ABC Goal Achievement

	Met all goals (n=39)	Met some goals (n=478)	Met no goals (n=127)	p-value
Age (years)	34 ± 7	36 ± 9	38 ± 9	0.06
Sex (male %)	21%	43%	61%	<0.0001
Diabetes duration (years)	23 ± 8	23 ± 9	23 ± 8	0.74
HbA1c (%)	6.5 ± 0.4	7.9 ± 1.2	8.7 ± 1.2	<0.0001
LDL-C(mg/dL)	76 ± 15	95 ± 26	130 ± 23	<0.0001
HDL-C (mg/dL)	56 ± 13	57 ± 17	54 ± 14	0.14
Triglycerides (mg/dL)	63 ± 1	80 ± 2	99 ± 2	<0.0001
Systolic BP (mm Hg)	107 ± 10	115 ± 13	127 ± 14	<0.0001
Diastolic BP (mm Hg)	70 ± 6	76 ± 8	85 ± 7	<0.0001
BMI (kg/m ²)	25.4 ± 3.1	26.0 ± 4.4	27.2 ± 4.4	0.01
Waist circumference (cm)	80.2 ± 10.3	84.2 ± 12.1	89.9 ± 13.1	<0.0001
AER (µg/min)	4.3 ± 2.2	9.6 ± 4.4	19.2 ± 6.7	<0.0001
eGFR _{CYSTATIN C}	111 ± 14	106 ± 22	103 ± 24	0.10
On antihypertensive medications at baseline (%)	23%	36%	48%	0.007
Ever smoker (% yes)	21%	20%	23%	0.68

Data are means ± SD or %

Table 2

Goal Achievement and Micro- and Macrovascular Complications over 6-years

	Microvascular complications over 6-years (n=99)		CACp over 6-years (n=199)	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI) *	Unadjusted OR (95% CI)	Adjusted OR(95% CI) *
No goals vs. some goals	3.6 (2.0–6.5) P<0.0001	3.5 (1.8–6.7) P=0.0002	1.7 (1.0–2.7) P=0.04	1.0 (0.5–1.8) P=0.21
No goals vs. all goals	8.5 (2.3–31.5) p=0.001	6.5 (1.6–26.3) P=0.009	1.7 (0.8–3.9) P=0.19	1.8 (0.6–5.0) P=0.29

* Adjusted for age, sex, duration, BP meds, statins, smoking and BMI

** Adjusted for age, sex, duration, BP meds, statins, smoking, BMI and baseline CAC