Clinical trial design

Appropriate Blood Pressure Control in NIDDM (ABCD) Trial

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Summary The ABCD (Appropriate Blood Pressure Control in Diabetes) Trial is a large, prospective, randomized clinical trial of 950 patients with non-insulin-dependent diabetes mellitus (NIDDM) designed to compare the effects of intensive blood pressure control with moderate control on the prevention and progression of diabetic nephropathy, retinopathy, cardiovascular disease, and neuropathy in NIDDM. The secondary objective is to determine equivalency of the effects of a calcium channel blocker (nisoldipine) and an angiotensin-converting-enzyme inhibitor (enalapril) as a first-line antihypertensive agent in the prevention and/or progression of these diabetic vascular complications. The study consists of two study populations aged 40–74 years, 470 hypertensive patients (diastolic blood pressure of ≥ 90.0 mmHg at time of randomization) and 480 normotensive patients (diastolic blood pressure of 80.0 mmHg at time of randomization). The study duration is 5 years and is scheduled to end in May of 1998. Patients are randomized to receive either intensive antihypertensive drug therapy or moderate antihypertensive drug therapy. Patients are also randomized to nisoldipine or enalapril, with open-label medications added if further blood pressure control is necessary. The primary outcome measure is glomerular filtration rate as assessed by 24-h creatinine clearance. Secondary outcome measures are urinary albumin excretion, left ventricular hypertrophy, retinopathy, and neuropathy. Cardiovascular morbidity and mortality will also be evaluated. Given the data showing the impact of hypertension on complications in NIDDM, the ABCD Trial is designed to determine if intensive antihypertensive therapy will be more efficacious than moderate antihypertensive therapy on the outcome of diabetic complications in NIDDM. [Diabetologia (1996) 39: 1646–1654]

Keywords Hypertension, Diabetes, Non-insulin dependent

There is considerable epidemiologic evidence suggesting that hypertension plays a significant role in the development and progression of diabetic nephropathy [1], retinopathy [2, 3], cardiovascular disease [4–7], and neuropathy [8] in patients with non-insulin-

dependent diabetes mellitus (NIDDM). Furthermore, several studies have demonstrated a significant increase in mortality in diabetic patients with hypertension [9, 10]. Although the epidemiological evidence demonstrating the strong association between hypertension and diabetic vascular complications is compelling, no intervention studies have been done to evaluate the efficacy of antihypertensive therapy in preventing these complications in patients with NIDDM. The absence of intervention studies in the NIDDM population is particularly remarkable, since NIDDM patients account for more than 90% of all diabetic patients [11] and 60% of diabetic end-stage renal disease in the United States. Moreover, end-stage renal disease secondary to diabetes costs the

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Abbreviations: ABCD, Appropriate Blood Pressure Control in Diabetes; NIDDM, non-insulin-dependent diabetes mellitus; IDDM, insulin-dependent diabetes mellitus; RDBP, randomization diastolic blood pressure; ACE, angiotensin converting enzyme; PE, parameter estimate; UAE, urinary albumin excretion; ABI, ankle/brachial indices; DCCT, Diabetes Control and Complications Trial.

health care system over three billion dollars annually [12].

The beneficial effect of antihypertensive therapy on diabetic renal disease has been demonstrated in animal studies [13] and in insulin-dependent diabetic (IDDM) patients [14]. Lewis et al. [15] also demonstrated that the use of captopril in IDDM patients can delay the progression of diabetic nephropathy independent of blood pressure control. Although the evidence for blood pressure control and the use of angiotensin-converting-enzyme inhibitors in IDDM for diabetic nephropathy is compelling, their role in the NIDDM population is less certain [16]. The Appropriate Blood Pressure Control in Diabetes (ABCD) Trial is a large, prospective, randomized clinical trial designed to determine the effect of intensive compared to moderate blood pressure control on the prevention and occurrence of diabetic vascular complications in NIDDM.

The ABCD Trial includes two study populations, hypertensive NIDDM subjects and normotensive NIDDM subjects, who will be analysed separately. In each population, the effect of intensive compared to moderate blood pressure control will be evaluated with respect to preventing the development and/or progression of diabetic renal disease, retinopathy, cardiovascular disease and neuropathy.

Study design

The ABCD Trial is a prospective, controlled, randomized trial based in Denver, Colorado, USA. The study populations are a group of normotensive NIDDM subjects (randomization diastolic blood pressure (RDBP) of 80.0–89.9 mmHg) and a group of hypertensive NIDDM subjects (RDBP $\geq$ 90.0 mmHg). The ABCD Trial has been described in detail previously [17, 18]. The RDBP is determined by averaging the mean diastolic blood pressure of the randomization visit and the visit preceding the randomization visit. The design of the normotensive and hypertensive protocols are shown in Figure 1. For the normotensive population, the goal of intensive antihypertensive therapy is to reduce the RDBP by 10 mmHg. In this population, the goal for moderate antihypertensive therapy is to maintain the RDBP. For the hypertensive population, the goal for intensive antihypertensive therapy is a diastolic blood pressure of 75.0 mmHg. The goal of moderate therapy for this population is a diastolic blood pressure of 89.0 mmHg. The effects of intensive compared to moderate antihypertensive therapy for each population will be evaluated with respect to preventing the development or progression of diabetic renal disease, retinopathy, cardiovascular disease and neuropathy.

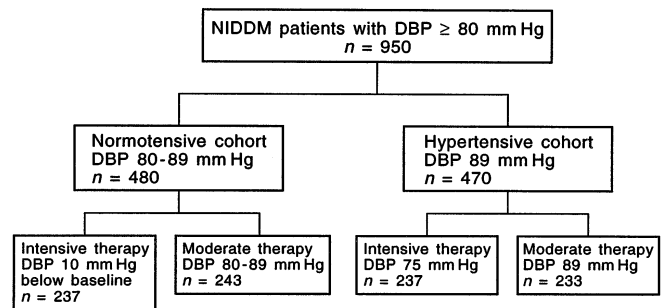The secondary objective of the study is to determine if there is equivalent benefit from a calcium

Fig. 1 Study design and randomizations of the ABCD trial. DBP, diastolic blood pressure

blocker (nisoldipine) compared to an angiotensin-converting-enzyme (ACE) inhibitor (enalapril) as a first-line antihypertensive medication in slowing the progression or delaying the onset of diabetic complications.

Methods

Individuals who passed the initial telephone screening were invited for an eligibility visit. At the eligibility visit, complete inclusion and exclusion criteria were reviewed. Individuals meeting the eligibility criteria and who gave informed consent were enrolled in the study. During the pre-randomization period of the trial, any pre-existing antihypertensive agents that participants may have been taking prior to study enrollment were tapered off and placebo was prescribed for a minimum of 7 to a maximum of 11 weeks. Patients meeting the criteria for early randomization (blood pressure exceeding 180/105 mmHg) were randomized and began receiving assigned treatment because of safety concerns. During the pre-randomization period all baseline data were obtained. The baseline data consisted of a full medical history and physical examination, blood samples (for fasting biochemical and lipid profiles, complete blood count, and glycated haemoglobin levels), 24-h creatinine clearance measurements, urinary albumin excretion rate, retinal photographs, exercise treadmill test, electrocardiogram, ankle/brachial index by doppler ultrasound and evaluation of diabetic neuropathy. Compliance was assessed by pill count and visit compliance.

Main outcome measure: glomerular filtration rate

During the pre-randomization period, the glomerular filtration rate was estimated by 24-h creatinine clearance (ml $\cdot$ min^{-1} $\cdot$ 1.73 m^2). All urine samples were screened for adequacy of collection using the 24-h total creatinine excretion value. Measurements for creatinine clearance are scheduled for every 6 months thereafter.

Secondary outcome measures:

Urinary albumin excretion (UAE) rate. UAE was measured from a 24-h collection at baseline and is measured every 6 months after randomization. During the first 8 months of the study, UAE was measured by the nephelometric method

[19] and by a radioimmunoassay technique thereafter (Double Antibody Albumin #KHD2; Diagnostic Products Corp, Los Angeles, Calif., USA). The correlation coefficient for the two methods was $r^2 = 0.99$. For the purposes of analyses, UAE is classified into one of the following categories: 1) no albuminuria (< 20 μg/min); 2) microalbuminuria (20–200 μg/min); and 3) overt proteinuria (> 200 μg/min) [20].

Retinopathy. Retinal photographs were taken by a technician at the Colorado Prevention Center at baseline and then scheduled at 2 and 5 years post-randomization. All retinal films are interpreted and staged at the Wisconsin Retinal Reading Center without knowledge of the group to which the patient has been randomized. Retinopathy is staged using the Modified Airlie classification criteria established by the Wisconsin Retinal Reading Center [21].

Diabetic Neuropathy. Neuropathy is assessed and staged according to the recommendations made by the American Diabetes Association and American Academy of Neurology at the San Antonio Conference on Diabetic Neuropathy [22]. Staging of neuropathy is based on neurological symptom scores, neurological disability scores, autonomic function testing and quantitative sensory examination. Neuropathy was evaluated at baseline and then scheduled at 2 and 5 years post-randomization.

Cardiovascular outcome measures. Cardiovascular events include: cardiac death, cerebrovascular death, myocardial infarction, congestive heart failure, coronary artery disease without myocardial infarction (documented by angiogram), cerebrovascular accident, atherosclerotic complications (aortic dissection, atherosclerotic arterial aneurysm, and mesenteric ischaemia or infarction), angina and serious ventricular arrhythmias. An Endpoint Committee blinded to randomization assignment will ascertain the diagnosis of myocardial infarction, cerebrovascular accident, congestive heart failure and sudden death based on all available pertinent information.

Electrocardiograms (ECG) were obtained at baseline and are being performed every 6 months post-randomization. ECGs are evaluated for abnormalities consistent for Q-wave myocardial infarctions and for left ventricular hypertrophy according to the Estes criteria [23], the Sokolow voltage criteria [24], and the Cornell [25] gender-specific voltage criteria.

Exercise treadmill tests using a half-Bruce Protocol were performed at baseline and then scheduled at 2 and 5 years post-randomization to evaluate exercise-induced cardiac ischaemia. The ECG responses are classified as: 1) non-ischaemic; 2) ischaemic, ≥ 1 mm of horizontal or downsloping ST segment depression from the resting ECG; or 3) non-diagnostic, i. e. peak heart rate less than 85 % of the predicted maximum heart rate (220 minus age in years).

Ankle/brachial indices (ABI) were utilized to evaluate peripheral vascular disease at baseline and at 2 and 5 years post-randomization. ABIs were obtained by Doppler as adapted by Hiatt et al. [26]. An abnormal ABI is defined as 0.94 or less.

Laboratory measurements. Blood samples were obtained at the Colorado Prevention Center and evaluated by National Health Laboratories, Inc. (Englewood, Colorado, USA). Fasting blood samples were obtained at baseline and then 6 months' post-randomization for glucose, glycated haemoglobin, sodium, potassium, chloride, bicarbonate, creatinine, total protein, albumin, phosphorus, calcium, uric acid, alkaline phosphatase, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, lactic dehydrogenase, total cholesterol, triglyceride, high-density (HDL) cholesterol and low density

(LDL) cholesterol. Additional haematologic measurements, including leukocyte count, haemoglobin, haematocrit and platelet values were performed at baseline and then every 6 months post-randomization.

Patients. A total of 2329 NIDDM patients, primarily from the Denver metropolitan area, underwent an eligibility visit for the ABCD Trial. Of these 1379 patients were found to be ineligible; therefore 950 patients were randomized for the study. Of the patients 61 % are male. The average age at baseline was 58 ± 0.5 (SEM) years with a range of 40 to 74 years. The average ages of the 470 patients in the hypertensive population and the 480 patients in the normotensive population were 57 ± 0.5 years and 59 ± 0.5 years, respectively. The duration of hypertension for the hypertensive population was 11.5 ± 0.5 years with a duration of diabetes of 8.5 ± 0.3 years. In the normotensive population, the duration of diabetes was 8.9 ± 0.3 years. There were no significant differences in age, duration of diabetes, glycated haemoglobin level, body mass index, and duration of hypertension between the intensive and moderate antihypertensive therapy groups for the normotensive and hypertensive populations (Table 1).

The racial and ethnic composition of all the patients in the ABCD Trial is 70 % non-Hispanic white, 15 % Hispanic, 11 % African-American, and 4 % other. Sixty-one percent of the patients in the study have smoked or are currently smoking; the average number of pack-years of the patients at the time of entrance into the study was 19 ± 0.9. Fifty-one percent are in full-time employment and 38 % have attended at least 1 year of college. The baseline characteristics of the ABCD Trial have been discussed in detail in a previous paper [27].

We have done cross-sectional studies evaluating the possible relationships between various clinical characteristics at entry to the study with prevalence of diabetic complications.

Urinary albumin excretion. As noted, the estimated annual cost of diabetic nephropathy is over three billion dollars [12] in the United States. NIDDM causes 60 % of the end-stage renal disease secondary to diabetic nephropathy. Thus far, studies evaluating diabetic nephropathy have focused mainly on IDDM subjects [15, 28, 29]. In addition, long-term prospective studies have also determined that UAE, specifically microalbuminuria, is a powerful predictor for the future development of diabetic nephropathy and retinopathy in IDDM [29, 30, 31]. Presently only a few studies, performed mainly on homogeneous Caucasian European NIDDM populations have demonstrated an association between microalbuminuria and an increased incidence of cardiovascular events [31–33] and retinopathy [34]. At this time there have been no studies performed in the United States that have evaluated the relationship of microalbuminuria with retinal, neurological and cardiovascular complications in NIDDM.

This is the first study of its kind to be done in the United States involving African-American, Hispanic and non-Hispanic white NIDDM subjects from a large metropolitan area. Although 90 % of all diabetic patients have NIDDM, the prognostic value of microalbuminuria in this setting and the associated risk factors are less well known than in IDDM patients. Against this background, the class of UAE was correlated with fasting blood glucose, glycated haemoglobin, systolic and diastolic blood pressure, lipid profile, age, gender, duration of diabetes, duration of hypertension, history of cardiovascular disease, race and ethnicity, smoking status, body mass index (BMI) and mode of hypoglycaemic therapy. A cross-sectional analysis was also undertaken in the same NIDDM subjects to examine possible relationships of UAE with diabetic vascular complications which included retinopathy, neuropathy and

Table 1. Baseline patient characteristics of randomized participants in the ABCD trial

	Hypertensive		Normotensive	
	Intensive	Moderate	Intensive	Moderate
n	237	233	237	243
Age (years)	57.5 ± 0.5	57.2 ± 0.5	58.5 ± 0.6	59.1 ± 0.5
Male (%)	67.0	68.0	53.0	56.0
Duration diabetes (years)	8.7 ± 0.5	8.2 ± 0.4	8.7 ± 0.5	9.1 ± 0.5
Duration hypertension (years)	11.7 ± 0.7	11.3 ± 0.6	NA	NA
Prior history of cardiovascular disease (%)	13.9	12.9	10.5	14.0
Glycated haemoglobin (%)	11.7 ± 0.2	11.5 ± 0.2	11.5 ± 0.2	11.6 ± 0.2
Body mass index (kg/m^2)	31.7 ± 0.3	31.7 ± 0.4	31.7 ± 0.4	31.4 ± 0.4
Current smokers (%)	11.8	15.9	13.1	13.2
Systolic blood pressure at randomization (mm Hg)	156.1 ± 1.1	154.9 ± 1.2	135.6 ± 0.9	137.8 ± 1.0
Diastolic blood pressure at randomization (mm Hg)	98.0 ± 0.4	97.8 ± 0.4	84.4 ± 0.2	84.4 ± 0.2
Race (%)				
Non-Hispanic White	66.2	66.5	75.9	72.4
African-American	15.6	18.5	6.8	7.4
Hispanic	14.8	12.0	15.6	17.7
Oriental	2.5	1.3	0.4	1.2
Other	0.8	1.3	1.2	1.2
Creatinine clearance (ml $\cdot$ min^{-1} $\cdot$ l $\cdot$ 73m^{-2})	83.7 ± 1.8	85.0 ± 1.9	84.0 ± 1.6	82.5 ± 1.6
Urinary albumin excretion (μg/min)	246.9 ± 39.6	213.5 ± 34.9	97.7 ± 22.3	126.5 ± 25.0
Patients with retinopathy (%)	61	62	51	53
Patients with neuropathy (%)	43	46	41	46
Patients with abnormal ABIs (%)	11	12	16	19

Values are mean $\pm$ SEM

Table 2. Baseline anti-hypertensive medication for patients in the ABCD trial prior to randomization[a]

Type of anti-hypertensive medication	Frequency (Percentage of patients on the medication)
Diuretics	50 (48)
Beta blockers	27 (26)
Calcium channel blockers	1 (1)
Angiotensin converting enzyme inhibitor	6 (6)
Central α-agonist	23 (22)
Alpha blockers	14 (13)
Direct vasodilators	1 (1)

[a] 104 patients on 122 medications

cardiovascular disease. UAE was categorized and defined as follows:
1. normal microalbuminuria (NA) < 20 μg/min
2. microalbuminuria (MA) 20–200 μg/min
3. overt albuminuria (OA) > 200 μg/min

Methods. The analyses were performed on UAE as a categorical variable. Univariate analyses were performed to determine correlation coefficients between each of the risk factors and UAE. Chi-square analyses were performed to test for univariate associations between categorical risk factors and UAE status. For the evaluation of the diabetic complications, chi-square was computed for univariate tests of association between UAE status and the presence of diabetic complications which included diabetic retinopathy, cardiovascular disease, and neuropathy.

To determine the independent association of each of the risk factors, all variables were entered into a multiple logistic regression model. Controlling for diabetes duration, glycated haemoglobin, gender and race, risk factors found to be significant in the univariate analyses were used to determine if they possessed an independent association with the presence of MA or OA. To determine whether UAE was independently associated with the presence of diabetic retinopathy, cardiovascular disease and neuropathy, UAE was entered in multiple logistic regression models controlling for diabetes duration, hypertension duration, glycated haemoglobin, systolic and diastolic hypertension, age and gender. A separate analysis was performed for each of the diabetic complications.

Results

In the univariate analyses race/ethnicity, male gender, poor glycaemic control, insulin use, duration of diabetes, dyslipidaemia, diastolic and systolic hypertension, smoking and obesity were significantly correlated with MA and OA (Table 3). Univariate analyses revealed that UAE was significantly associated with the presence of retinopathy, neuropathy and cardiovascular disease (Table 3).

The factors found to be significantly associated with UAE status in the multivariate logistic regression analysis, controlling for diabetes duration, glycated haemoglobin, gender and race, were systolic

Table 3. Univariate analyses: baseline characteristics/complications with urinary albumin excretion status

	Normoalbuminuria (NA) < 20 μg/min	Microalbuminuria (MA) 20–200 μg/min	Overt albuminuria (OA) > 200 μg/min	p value
Gender (male/female)	303/239	179/96	94/36	
Age (years)	58.0 ± 0.4	58.8 ± 0.5	58.5 ± 0.7	NS
Duration of diabetes (years)	8.1 ± 0.3	9.2 ± 0.4	11.2 ± 0.6	b, c
Duration of hypertension (years)	8.7 ± 0.4	10.2 ± 0.6	10.1 ± 0.9	NS
Fasting glucose (mmol/l)	10.3 ± 0.2	11.3 ± 0.2	11.4 ± 0.3	a, b
Glycosylated hemoglobin	11.1 ± 0.14	12.1 ± 0.19	12.6 ± 0.28	a, b
Fasting cholesterol (mmol/l)	5.50 ± 0.05	5.89 ± 0.20	6.00 ± 0.22	NS
Fasting triglycerides	237 ± 7.9	307 ± 19.3	406 ± 7.9	a, b, c
HDL (mmol/l)	1.08 ± 0.01	1.04 ± 0.02	1.00 ± 0.03	b
Cholesterol/HDL	5.5 ± 0.08	6.0 ± 0.2	6.4 ± 0.3	a, b
Fasting LDL (mmol/l)	3.32 ± 0.04	3.37 ± 0.06	3.55 ± 0.10	NS
Body mass index (kg/m^2)	29.7 ± 0.3	31.0 ± 0.4	32.1 ± 0.6	b
Minimal Waist/Maximal	0.92 ± 0.7	0.94 ± 0.07	0.95 ± 0.07	a, b
Neuropathy[e]	36%	48%	68%	
Retinopathy[f]	51%	62%	75%	d
Cardiovascular disease	40%	48%	58%	

[a] $p < 0.05$ NA vs MA, [b] $p < 0.05$ NA vs OA, [c] $p < 0.05$ MA vs OA. [d] Chi-square analyses were performed evaluating the percentage of patients with various diabetic complications as it relates to increasing urinary albumin status, $p < 0.001$ for all complications. [e] Four patients did not perform the neurology exam. [f] Fifty-five patients either had ungradable or were unable to perform the retinal photographs. Data are mean ± SEM

Table 4. Multiple logistic regression analyses for diabetic complications with regard to increasing urinary albumin excretion stage[a]

Diabetic complication	Odds ratios	95% Confidence interval	p-value
Retinopathy	1.61	1.05–1.65	0.0190
Neuropathy	1.62	1.32–1.99	0.0001
Cardiovascular disease	1.27	1.03–1.55	0.0222

[a] The multiple logistic regression analysis for each complication was controlled for age, diabetes duration, duration of hypertension, gender, systolic and diastolic hypertension, and glycated haemoglobin

hypertension (odds ratio (OR) = 2.16; 95% confidence interval, CI, = 1.49, 3.13; $p = 0.0001$), pack-years of smoking (OR = 1.07 per 10 pack-years, 95% CI = 1.02, 1.13; $p = 0.02$), increasing BMI (OR = 1.26 per 5 kg/m^2 increase, 95% CI = 1.09, 1.45; $p = 0.002$), decreasing HDL cholesterol (OR = 1.16 per 10 mg/dl decrease, 95% CI = 1.01, 1.33; $p = 0.04$), and insulin use (OR = 1.53, 95% CI = 1.09, 2.15; $p = 0.02$).

In the multiple logistic regression analyses, controlling for diabetes duration, hypertension duration, glycated haemoglobin, systolic and diastolic hypertension, age and gender, an increase in UAE stage was independently associated with the presence of retinopathy, neuropathy and cardiovascular disease (Table 4).

Exercise capacity. Cardiovascular disease accounts for 40% of the overall mortality in this country [35] and is the leading cause of mortality in the NIDDM population [36–38]. Rubler et al. [39] have demonstrated that poor exercise capacity is associated with an increase in cardiovascular events in diabetic subjects. Exercise capacity has also been utilized as a non-invasive parameter for predicting cardiovascular mortality in asymptomatic populations [40, 41], patients with coronary artery disease [42] and patients with congestive heart failure [43].

Previous studies have demonstrated that NIDDM patients have a reduced exercise capacity compared to age-matched normal subjects [39], but the factors for this decrease in exercise capacity are still unclear. The present study was therefore conducted on 453 NIDDM patients, 291 males and 162 females, who underwent a screening exercise test for the ABCD Trial to examine the possible risk factors that may influence exercise capacity. The NIDDM patients consisted of normotensive and hypertensive patients without a history of coronary artery disease and/or congestive heart failure. The study examined potential correlates of excercise capacity such as age, diabetes duration, metabolic control, degree and duration of hypertension, race and ethnicity and smoking habits.

Methods. Univariate analyses were performed separately for males and females relating peak oxygen consumption to resting systolic and diastolic blood pressures, metabolic parameters, smoking, duration of diabetes, duration of hypertension, and demographics. Regression analysis was performed in the case of continuous independent variables, and chi-square tests were used with discrete variables. Multiple regression analyses that included those variables, significantly related to peak oxygen consumption in the univariate tests, were performed separately for each gender.

Table 5. Univariate analyses of baseline characteristics with exercise capacity as reflected by peak VO_2

Patient characteristics	Males ($n = 283$)			Females ($n = 147$)		
	Mean peak VO_2 (mean ± SEM)	r	p-value	Peak VO_2	r	p-value
Age (years)	58.2 ± 0.5	− 0.3	< 0.0001	57.3 ± 0.6	− 0.2	< 0.0001
Number of patients with hypertension (%)	187 (66)	T	< 0.02	90 (61)	T	< 0.0004
Duration of hypertension (years)	8.4 ± 0.6	− 0.1	< 0.8	11.6 ± 0.9	− 0.2	< 0.05
Duration of diabetes (years)	8.9 ± 0.4	0.01	< 0.8	8.7 ± 0.5	− 0.09	< 0.3
Fasting glucose (3.61–6.40 mmol/l)[b]	10.30 ± 0.22	− 0.04	< 0.5	11.21 ± 0.31	0.07	< 0.04
Glycated Hb (0.55–0.82 % fraction of 1.00)[b]	0.11 ± 0.0002	− 0.1	< 0.1	0.12 ± 0.003	0.06	< 0.5
Cholesterol (3.36–5.17 mmol/l)[b]	5.51 ± 0.02	− 0.1	< 0.09	6.07 ± 0.34	− 0.1	< 0.2
HDL (Males: 0.77–1.94 mmol/l)[b] (Females: 1.03–2.33 mmol/l)[b]	1.00 ± 0.02	0.05	< 0.4	1.06 ± 0.03	− 0.02	< 0.8
LDL (< 3.36 mmol/l)[b]	3.36 ± 0.05	− 0.14	< 0.6	3.36 ± 0.08	0.00	< 1.0
Triglyceride (0.34–1.69 mmol/l)[b]	3.02 ± 0.04	− 0.04	< 0.5	3.02 ± 0.06	− 0.08	< 0.4
Body mass index (kg/m²)	30.2 ± 0.3	− 0.3	< 0.0001	31.9 ± 6.0	− 0.4	< 0.0001
Systolic blood pressure (mmHg)	144.0 ± 1.1	− 0.2	< 0.0001	142.0 ± 1.5	− 0.2	< 0.007
Diastolic blood pressure (mmHg)	88.3 ± 0.7	− 0.08	< 0.2	91.0 ± 0.5	− 0.1	< 0.08
Pack years smoking	24.7 ± 1.9	− 0.2	< 0.02	8.9 ± 1.4	− 0.2	< 0.02

Patients not categorized to non-Hispanic whites, Hispanic whites, or African-Americans were not included in the table. Values are means ± SEM. n, Number of subjects. [a] T, t-test performed on patients without and with hypertension (males: 24.9 ± 0.6 vs 23.2 ± 0.3; females: 20.2 ± 0.5 vs 17.7 ± 0.4 ml · kg⁻¹ · min⁻¹). [b] Normal values as reported by National Health Laboratories, Inc. r, correlation coefficient. NS, $p > 0.05$

Results Table 5 lists the selected patient characteristics examining their associations with peak VO_2. Of these, an increase in body mass index, an increase in systolic blood pressure, and an increase in pack-years smoked were significantly associated with a decrease in exercise capacity.

The multiple linear regression analyses for each gender revealed that in males, age (parameter estimate (PE) = –0.16/years; CI = –0.23, –0.09; $p = 0.0001$), body mass index (PE = –0.41 · kg⁻¹ · m⁻²; CI = –0.52, –0.29; $p = 0.0001$), systolic blood pressure (PE = –0.03/mmHg, CI = –0.06, –0.01; $p = 0.05$), pack-years smoking (PE = –0.02/pack years; CI = –0.04, –0.01; $p = 0.01$) and the African-American race (PE = –2.50; CI = –4.28, –0.70; $p = 0.006$) were independently associated with a decrease in exercise capacity (Table 7). A similar finding was found for females, age (PE = –0.17/years; CI = –0.24, –0.11; $p = 0.0001$), body mass index (PE = –0.39 · kg⁻¹ · m⁻²; CI = –0.48, –0.31; $p = 0.0001$), systolic blood pressure (PE = –0.03/mmHg; CI = –0.06, –0.01; $p = 0.05$), pack-years smoking (PE = –0.04/pack years; CI = –0.07, –0.01; $p = 0.003$) and the African-American race (PE = –2.96; CI = –4.45, –1.47; $p = 0.0002$).

Discussion

The baseline period enabled collection of valuable information concerning characteristics of NIDDM patients. The cross-sectional evaluations performed thus far have revealed that: 1) various potentially reversible factors are associated with the presence of microalbuminuria and overt albuminuria; 2) increasing UAE is associated with micro- and macrovascular diabetic complications; and 3) various factors are associated with decreased exercise capacity in NIDDM.

In the present study, the presence of microalbuminuria or overt albuminuria were independently related with the presence of retinopathy, neuropathy, and cardiovascular disease in a large cohort of NIDDM patients living in a metropolitan area in the United States. The association between these diabetic complications and UAE demonstrated in the present study supports the theory that increased UAE may represent generalized vascular damage as has been proposed by Deckert et al. [44] who observed similar findings in an IDDM population. Previous studies examining the association of albuminuria with diabetic retinopathy have been conflicting [35, 45–47], but we

believe that the large number of patients included in the present study enabled us to adequately obtain a significant amount of power to evaluate this association.

The association of albuminuria with the presence of neuropathy has been demonstrated in a number of studies involving IDDM subjects [48, 49], but this is the first demonstration in patients with NIDDM. Although the exact pathogenesis of diabetic neuropathy is still under question, morphological studies suggest that an ischaemic aetiology is involved in the pathogenesis of diabetic polyneuropathy [50]. Thus, if a generalized vascular insult increases UAE rates, it is arguable that the same pathogenic mechanism is occurring at the level of the small epineural vessels supplying the nerves.

Cardiovascular complications are the leading cause of death in NIDDM [36–38]. In the present study the presence of cardiovascular disease was independently associated with an increase in UAE. These results complement those of Mogensen [51], who found in a 10-year follow-up study that the survival of NIDDM patients with microalbuminuria was 4.7 % as compared to 54 % in NIDDM patients without microalbuminuria.

To help understand how the progression of diabetic nephropathy can be slowed in this NIDDM population, we evaluated the possible risk factors associated with increasing UAE stage. The factors included poor metabolic control as reflected by increasing glycated haemoglobin, systolic hypertension, body mass index, decreasing HDL, smoking and insulin therapy. As we have previously explained [52], a number of these factors are potentially reversible with aggressive intervention. Recently, the Diabetes Control and Complications Trial (DCCT) [26] showed that tight glycaemic control can reverse and prevent diabetic nephropathy as represented by microalbuminuria. However, the role of glycaemic control in the pathogenesis of microalbuminuria in the NIDDM population is less certain since there are some conflicting data [53–55]. Consequently, as hyperglycaemia may be difficult to treat in insulin-resistant NIDDM subjects, it is important to consider other therapeutic options. Cross-sectional investigations, such as the present study, lend insight into significant associations between complications such as microalbuminuria and risk factors. The outcome of such observations can be indicative of the need for appropriate interventional trials. As an increase in UAE may be an indication of generalized vascular injury, early aggressive intervention of these risk factors may have the potential of altering the natural history of not only renal disease, but also of other vascular complications associated with NIDDM.

Also as part of the baseline correlations, we examined the possible associations of various baseline characteristics with exercise capacity. As discussed previously, exercise capacity has been used as a reliable non-invasive predictor of cardiac events [40–43] in non-diabetic patients. The present study demonstrated that multiple cardiac risk factors, specifically age, obesity, systolic hypertension, smoking, and race, are independently associated with an impairment of exercise capacity in this NIDDM population. The implications of these findings are important since a decrease in exercise capacity may impact a diabetic patient's ability to perform normal daily activities and potentially be associated with a higher cardiac morbidity and mortality. With the exception of age and race, the factors associated with impairment of exercise capacity are conceivably reversible. In a previous study, we also found that hypertension, and possibly left ventricular hypertrophy, may impact exercise capacity more in African-Americans with NIDDM than their Hispanic and non-Hispanic white counterparts [56]. As in the findings with diabetic nephropathy, aggressive interventions may potentially play a role in improving exercise capacity and potentially improve the increased cardiovascular mortality with which it is associated.

This prospective, randomized, interventional clinical trial is important for several reasons. Diabetes and its complications cause morbidity and mortality in the United States that costs the health system nearly 100 billion dollars per year [57]. As demonstrated in these baseline correlations, hypertension appears to be a significant contributor to the development and progression of diabetic complications. Most interventional studies performed on diabetic complications thus far have involved only subjects with IDDM, even though NIDDM accounts for more than 90 % of the diabetic patients in the United States. The ABCD Trial will compare the effect of intensive compared to moderate control of diastolic blood pressure in a hypertensive and a normotensive population on renal function, retinopathy, cardiovascular disease, and neuropathy. In addition, any differential effects of an ACE inhibitor and a calcium channel blocker on these complications will be studied. Hence, the ABCD Trial will determine if hypertension should be considered at a lower level in the NIDDM population to prevent vascular complications than the levels set by the conventional standards of hypertension (140/90 mmHg) for the non-diabetic population.

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