Rationale and design of the Brazilian Diabetes Study: a prospective cohort of type 2 diabetes

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Abstract

Background.

Optimal control of traditional risk factors only partially attenuates the exceeding cardiovascular mortality of individuals with diabetes. Employment of machine learning (ML) techniques aimed at identification of novel features of risk prediction is a compelling target to tackle residual cardiovascular risk.

Objective.

To identify clinical phenotypes of T2D which are more prone for developing cardiovascular disease.

Methods.

The Brazilian Diabetes Study is a single-center, ongoing, prospective registry of T2D individuals. Eligible patients are 30 years-old or older, with a confirmed T2D diagnosis. After an initial visit for signature of informed consent form and medical history registration, all volunteers undergo biochemical analysis, echocardiography, carotid ultrasound, ophthalmologist visit, dual x-ray absorptiometry, coronary artery calcium score, polyneuropathy assessment, advanced glycation end-products reader, and ambulatory blood pressure monitoring. A 5-year follow-up will be conducted by yearly phone interviews for endpoints disclosure. The primary endpoint is the difference between ML-based clinical phenotypes in the incidence of a composite of death, myocardial infarction, revascularization, and stroke. Since June/2016, 1030 patients (mean age: 57 years, diabetes duration of 9.7 years, 58% male) were enrolled in our study. Mean follow-up time was 3.7 years in October/2021.

Conclusions.

The BDS will be the first large population-based cohort dedicated to the identification of clinical phenotypes of T2D at higher risk of cardiovascular events. Data derived from this study will provide valuable information on risk estimation and prevention of cardiovascular and other diabetes-related events.

ClinicalTrials.gov Identifier:

NCT04949152

Introduction

The steady increase in the global prevalence of diabetes, currently estimated to be as high as 463 million individuals, has fueled the burden of cardiovascular disease and other diabetes-related complications.[1] In fact, compared to nondiabetics counterparts, individuals with diabetes have a 2-fold increased cardiovascular mortality, and a 4-fold increased risk of peripheral vascular disease and limb amputation.[2] In addition, diabetes, alongside hypertension, remains a major cause of end-stage kidney disease and blindness, thus entailing significant loss of quality-adjusted life years. [3,4]

In the past decades, prevention of diabetic complications has been chiefly grounded by the achievement of stricter control of traditional risk factors, such as glycated hemoglobin, low-density-lipoprotein cholesterol, and blood pressure.[5,6] Though reasonable, this strategy does not fully address the complex, multifactorial pathophysiology of diabetes.[7] As a matter of fact, cardiovascular mortality remains augmented even among individuals with optimal metabolic control.[8] Thereafter, growing attention has been directed to the development of risk prediction models dedicated to early detection of individuals at higher risk of complications to whom earlier tailored clinical interventions yield the greater therapeutical benefit.[5]

In this context, employment of artificial intelligence (AI) tools has been pursued as a compelling strategy intended to refine the accuracy of existing risk equations and ascertain novel features of risk prediction.[9–11]Machine learning (ML) models showed better accuracy than current algorithms, which are based on regression models from large clinical studies,for predicting outcomes, such as diabetic retinopathy[12], limb amputation[13], hospitalization for heart failure[14] and hypoglycemia[15,16]. ML-based algorithms also forecasted avoidable costs, increasing relevance for cost-effectiveness analysis of novel antidiabetic drugs to face the sharply rising diabetes-related global healthcare expenditures.[17] Moreover, data-based hierarchical clustering identified subgroups of patients with newly diagnosed diabetes more prone to develop chronic kidney disease and retinopathy.[18] Despite all these advances, whether these models accurately identify those at higher risk of atherosclerotic cardiovascular disease remains unanswered.

To address this unmet challenge, we designed the Brazilian Diabetes Study (BDS) as a population-based, prospective, ongoing cohort of adults with T2DM. Participants have been enrolled in in-depth clinical evaluation, biochemical analysis, and advanced cardiac imaging exams. Since June/2016, the BDS has enrolled 1030 participants who are currently undergoing annual appointments to assess predefined outcomes. The main goal is to identify clinical phenotypes of T2DM which are more prone for developing cardiovascular disease. Furthermore, the dataset derived from this cohort may be an insightful source of information on current treatment status and mayprovide ML-based models with data for generating novel risk estimate algorithms and cost-effectiveness analysis of clinical interventions.

Materials And Methods

Study design and participants

The Brazilian Diabetes Study is a prospective, ongoing, single-center, cohort of T2DM (clinicaltrials.gov: NCT04949152). Clinical and laboratory analyses are performed by the Atherosclerosis and Vascular Biology Laboratory (Aterolab), situated at the Clinical Research Center at the University of Campinas (Unicamp), Brazil. Social media and newspaper campaigns to boost recruitment are implemented. Eligible participants are 30 years-old or older, from both sexes, with a confirmed diagnosis of T2DM according to latest ADA criteria.[19] The study was approved by the local ethics committee (CAAE: 89525518.8.1001.5404) and complied to the Declaration of Helsinki principles.[20]

Eligible patients are invited to the research center for an explanation of the study protocol. After signing the informed consent form, participants have their demographical, anthropometrical, and medical history registered and are examined by a licensed doctor. After this visit, the following exams are scheduled: blood and urine sample collection; ambulatory blood pressure monitoring; advanced-glycation end-products measurement; echocardiogram; carotid ultrasound; flow-mediated dilation; ophthalmologic evaluation; dual X-ray absorptiometry; bone densitometry; handgrip strength; usual gait speed test; and coronary artery calcium score. Then, participants are contacted yearly for 5 years by detailed telephone interviews for endpoints disclosure.

The clinical research data management was based on the Research Electronic Data Capture (REDCap, Vanderbilt, USA) platform. Access to this system is restricted to investigators and the exportation of data for analysisis deidentified to protect individual's confidentiality. All researchers have been equally responsible for the obtainment and storage of information collected throughout this research. Results from both image and biochemical analysis are stored in this system and backed up to a dedicated storage rack remotely at the Unicamp data center. A dedicated investigator is responsible for generating a summary of exams' results and their delivery to participants.

Study protocol

First visit. On this occasion, participants are interviewed by a licensed physician for whole medical history taking. Information regarding the time since diagnosis of diabetes, medications in use, and comorbidities are registered. The race is self-reported. Participants are considered as having established cardiovascular disease if they presented any of the following: coronary heart disease, cerebrovascular disease, or peripheral artery disease. Subjects then undergo a complete physical examination, including registration of waist circumference, weight, height, and body mass index. Socioeconomic status is registered as years of study and current family income. Physical activity, as minutes and daily frequency per week, is also registered. In addition, at least 3 different phone numbers are recorded for follow-up.

Blood pressure measurement. Blood pressure measurements are performed using the HEM-7113, Omron Healthcare (São Paulo, Brazil) device according to the latest guidelines.[21] After 3 min resting, three consecutive measures are obtained with the patient sitting, and then standing, and the mean value of the last two measures for each position are considered. Orthostatic hypotension is diagnosed when a systolic blood pressure difference is $\geq$ 20 mmHg, or diastolic blood pressure difference is $\geq$ 10mmHg, is found between sited and upward measurements.

Electrocardiogram. A digital 15-min electrocardiogram was performed using the WinCardio (Micromed Surface Digital Electrocardiogram, Brazil). This software allowed further heart rate variability analysis.

Diabetic distal polyneuropathy. Diabetic distal polyneuropathy (DDP) is evaluated according to The Michigan Neuropathy Screening Instrument (MNSI), as previously validated.[22,23] In short, patients answer a 15-question survey on DDP-related symptoms. Later, they undergo a lower extremity examination to assess of neurological reflexes and tactile and vibratory sensitivity. Each abnormal finding scores 0.5 or 1, and scoring above 7 in the questionnaire, or 2.5 in the physical examination, has positive and negative predictive values of 84 and 73%, respectively.[24]

Ambulatory Blood Pressure Monitoring. Ambulatory Blood Pressure Monitoring (ABPM) is executed using the 90207 Spacelabs Healthcare (Washington, USA) an automated, according to the latest ESC guidelines.[25] This exam allowed the identification of white-coat hypertension, defined as elevated blood pressure values in the office, but normal readings out of this setting. Furthermore, this exam permitted the diagnosis of masked hypertension, defined as elevated values on daily routine measures, but normal blood pressure in the office. Blood pressure thresholds for hypertension are 140/90, 130/80, 135/85 and 120/70 mmHg for office blood pressure, 24h, day and night measures, respectively.[25] Other outcomes will include blood pressure variability and nocturnal dipping characterization.[26]

Blood and urine samples. After 12 h fasting, peripheral blood samples were obtained according to proper guidelines [27], centrifuged at 3500 rpm and analyzed for the following measurements: complete blood count, fasting glucose, glycated hemoglobin, lipid profile, triglycerides, thyroid-stimulating hormone, urea, creatinine, sodium, potassium, calcium, phosphorous, C-reactive protein, aspartate aminotransferase, alanine aminotransferase, ultrasensitive troponin T and brain-type natriuretic peptide. Glomerular filtration rate (Gfr) was estimated using the CKD-EPI equation. Urinalysis was also performed on the same day and analyzed for urinary albumin to creatinine and protein to creatinine ratio.

AgeReader ^{TM}. The autofluorescence reader (AGE Reader; DiagnOptics, Groningen, the Netherlands, serial number: 09-10138) illuminates a skin surface of ~4 cm^2, guarded against surrounding light, with an excitation light source with peak intensity at ~ 370 nm. Emission light and reflected excitation light from the skin area is measured with a spectrometer in the 300–600 nm range, using a glass fiber. Autofluorescence was computed by dividing the average light intensity of the emission spectrum 420–600 nm by the average light intensity of the reflected excitation spectrum 300–420 nm and expressed in arbitrary units (AU).[28] The measurements are performed in triplicate, and the average value is considered the definitive value of the AGE-Skin autoflurescence. AGE-Skin autofluorescence of all patients is assessed at the volar side of the arm, 10 cm below the elbow fold, in areas without tattoos, scars, cream or sunscreen.[28]

Echocardiography assessment. Transthoracic echocardiography is performed by fully licensed cardiologists with specialization in cardiovascular imaging, following technical recommendations and measurement techniques according to the latest American Society of Echocardiography guidelines.[29]

Heart scan images were acquired with a 1.5–4.5 MHz phased array transducer (Epiq CVX, Philips, Eindhoven, The Netherlands), and images processing with the Echo PAC software version 8.0 (GE Healthcare). Variable assessment and interpretation followed their respective guidelines: cardiac chambers diameters, chambers volumes, left ventricle (LV) mass, LV and right ventricular (RV) systolic function and global longitudinal, circumferential, and radial strain assessed by speckle tracking. For the LV diastolic function analysis, it considered tissue Doppler myocardial velocities, mitral wave inflow velocities, indexed left atrial volume and tricuspid regurgitation peak velocities as recommended in ASE guidelines.[30,31]

Carotid Doppler ultrasound. Trained cardiologists performed carotid Doppler ultrasound with a 5–13MHz linear array transducer (Epiq CVX, Philips, Eindhoven, The Netherlands). Briefly, the longitudinal image of the bilateral common, internal, and external carotid artery, and the vertebral artery, was scanned for atherosclerotic plaque detection, following ASE guidelines.[32] The carotid intima-media thickness (CIMT) was measured from the common carotid artery 20 mm from the carotid bulb and at least 10mm from the bifurcation using a semi-automated method. Carotid atherosclerosis was considered if participants presented any of the following: (i) atherosclerotic plaque, defined as a localized projection of more than 1.5mm into the lumen or thickening of 50% of the artery compared with an adjacent wall; (ii) IMT ≥ 1mm; or (iii) mean IMT above the 75th percentile, as previously determined for our population in the ELSA-Brazil study.[33]

Dual Energy X-Ray Absorptiometry (DXA). Body composition was assessed by Dual Energy X-Ray Absorptiometry (DXA). This technique is performed using the iDXA equipment model (GE Healthcare Lunar, Madison, WI, USA), with fan-beam detectors. After evaluation, data are analyzed using enCore™ 2011 software, version 13.60 (GE Healthcare Lunar, Madison, WI, USA). Trained professionals perform image acquisition and analysis according to the protocol previously described.[34] Furthermore, the positioning and placement of regions of interest (ROI) follow the manufacturer's recommended specifications. The DXA machines are maintained using standard quality control procedures, as recommended by the manufacturer.

Handgrip Strength. Handgrip strength is obtained with a manual hydraulic dynamometer (JAMAR Hydraulic Hand Dynamometer - Model PC-5030J1, Fred Sammons, Inc., Burr Ridge, IL: USA), respecting the protocol of the American Association of Hand Therapists. Briefly, the equipment is adjusted according to the size of the patient's hands. The subject is comfortably seated during the assessment, with feet flat on the floor, elbow flexed at 90 degrees, with shoulder and forearm in neutral rotation. An evaluation is performed three times on each hand and the result was calculated by the average of the three measurements, in kilograms (kg).

Usual Gait speed test. Usual gait speed test is performed on a surface with 10 meters of length, free from irregularities or obstacles. Four ground-referenced signaling are placed along the route: a starting point (0 meters / x feet), acceleration section (0-2 meters), measurement section (2-8 meters), deceleration section (8-10 meters), and arrival point (10 meters). During the test, the examiner activates the chronograph when

the subject's first foot touched the 2 meters mark and interrupts the measurement when the last foot exceeded 8 meters. The assessment is performed three times, with 1-minute intervals in-between. The final measure corresponds to the average speed of the three assessments.

Coronary artery calcium. Coronary artery calcium (CAC) is assessed by licensed doctors at the Department of Radiology of the Clinic Hospital of Unicamp. A computerized tomography scan is done with the validated image acquisition equipment BiographTM mCT (Siemens Healthcarengineers, Erlangen, Germany). Briefly, patients are subjected to a CT scan, making 3mm thick cuts limited to the cardiac area synchronized to the electrocardiographic tracings. Hypoattenuating calcifications of at least 130 Hounsfield units and areas > 3 pixels are considered, as previously recommended.[35]

Ophthalmologic evaluation. The ophthalmological evaluation measures the best-corrected visual acuity (BCVA), following the Snellen table adapted to 4 meters. Slit lamp biomicroscopy is performed and the lens status is defined following the LOCS III classification. After pupillary dilation with topical phenylephrine and tropicamide, patients are evaluated by a specialist retina ophthalmologist for possible findings of diabetic retinopathy. After clinical evaluation, patients are submitted to complementary examinations of retinography in a VISUCAM® device (NM/FA Carl Zeiss, USA) and Optical Coherence Tomography (OCT) using SPECTRALIS® SD-OCT (Heidelberg Engineering, Inc., USA) according to the following protocols: (i) posterior pole, for evaluation of retinal layers, measurement of central retinal thickness (CRT) and detection of possible changes caused by diabetes, such as macular edema; and (ii) seven lines and enhanced depth imaging method, for evaluation of choroidal thickness. CRT, assessed by OCT, is employed to detect, and classify diabetic macular edema in terms of distinct morphological features, as previously validated.[36,37]

Objectives

The general objective is to identify clinical phenotypes of T2DM which are more prone for developing cardiovascular disease.

Among the specific aims of the study are: (i) investigating the association between clinical features or biomarkers with clinical or subclinical cardiovascular disease; (ii) generate algorithms based on artificial intelligence intended to estimate the risk of diabetic-related events; (iii) elaborate a database for Markov-based modeling to estimate the cost-effectiveness of clinical interventions.

Cluster analysis

Cohort individuals are clustered based on similarity of their attributes. To achieve this goal, K-means clustering algorithm aimed at classifying each object of the dataset to their respective cluster based on randomization process (Random Forest) for positioning the initial cluster centers, or centroids, as close to optimal as possible. Based on previous studies, attributes are the following: age, diabetes duration, BMI, homoeostasis model assessment (HOMA) 2 estimates of β-cell function (HOMA2-B) and insulin resistance (HOMA2-IR).[18]k-means cluster is performed usingkmeansruns package in R version 3.3.1, and cluster stability is assessed by resampling the dataset 5000 times and computing Yule's Q coefficient.

Machine learning models

Machine learning techniques are employed to evaluate the main risk factors for cardiovascular outcomes. The following variables are considered as dependent: age, sex, years of study, income, diabetes duration, hypertension, LDL-C, CVD, BMI, smoking status, glycated hemoglobin (A1c), FBG, glomerular filtration rate (GFR), skin autofluorescence AGE reader, intima-media thickness in carotid ultrasound and lean-to-total mass. The independent variable is any major acute cardiovascular event (myocardial infarction, stroke, and revascularization). Other independent variables include microvascular complications, such as diabetic nephropathy (proteinuria or GFR < 60ml /min /1.73 m^2), diabetic retinopathy, and polyneuropathy; major adverse renal (doubling creatinine, GFR decline greater than 50% from baseline, treatment for end-stage kidney disease by dialysis or kidney transplantation, new-onset proteinuria) outcomes.

Discussion

The Brazilian Diabetes Study is the largest population-based diabetes cohort ever performed in a developing country. From June/2016 and July/2021, 1030 participants have been recruited, whose baseline characteristics are summarized in Table 2 (suppl. material). Other strengths are as follow: (i) the Brazilian Heart Study investigators, a group with a strong background in clinical research, collected the data; (ii) examinations include highly specialized tests performed with last-generation type of equipment by fully licensed doctors and trained cardiologists; (iii) in the future, data from this cohort may become a resource for hypothesis-generating and mechanistic studies on diabetes complications.

This study also has some limitations. More importantly, attending all steps of the study protocol will be time-consuming and may require an absence from work. This, conceivably, favors recruitment of highly motivated, and presumably more educated, individuals whose treatment and risk factors control tend to be enhanced. Moreover, we expect that most participants will be inhabitants of the metropolitan region where the research center is located. As this region presents a higher human development index when compared to national standards, higher income and private healthcare insurance coverage are expected. This potential bias should be borne in mind when generalizing our results to other Brazilian areas.

Statements And Declarations

Conflict of interest

The authors declare that there is no conflict of interest.

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Availability of data and materials

The Brazilian Diabetes Study investigators will hold intellectual property over data. Its availability may be considered upon reasonable request.

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Tables

Table 1. Study protocol and exams

Phase	Measurements
Visit 1	Informed consent form
	Questionnaire on demographical data
	Physical examination and anthropometry
	Blood pressure
	15 - min electrocardiogram
	Diabetic distal polyneuropathy
Visit 2	Blood sample and urinalysis
	Ambulatory blood pressure monitoring
	AGE reader
	Echocardiography
	Carotid ultrasound
	Ophthalmologist visit
	DXA
	Handgrip strength
	Usual gait speed
	Coronary artery calcium score
Yearly	Phone contact for outcomes

Table 2. Baseline data of participants

Demographics	
Age, years	57 ± 8.1
Male	611 (58.4)
Ethnicity (self-declared)	
Caucasian	708 (69.5)
Pardo	176 (17.3)
Black	115 (11.3)
Asian	19 (1.86)
Marital status	
Never married	101 (9.7)
Married/ stable union	711 (71.1)
Widowed/ divorced	185 (17.7)
Educational status	
Less than primary school	302 (28.9)
Completed primary school	371 (35.5)
Completed secondary school	296 (28.3)
University degree	59 (5.7)
Family income, tertiles	
< US$ 500	177 (16.9)
US$ 500 - 1000	226 (21.6)
≥ US$ 1000)	208 (19.9)
Labor status	
Working	439 (67,5)
Retired	163 (25,1)
Unemployed	48 (7,4)
Medical history	
Diabetes duration, years	9.7 ± 7.3
Hypertension, %	828 (80.1)
Dyslipidemia, %	764 (73)
CVD, %	382 (37.1)
Obese, %	428 (50.5)
Medications	
Anti-hypertensive, %	663 (63.4)
Lipid-lowering drugs, %	489 (46.7)
Aspirin, %	251 (24)
Oral glucose lowering, %	1015 (98.5)
Insulin	201 (19.5)
Biochemical analysis	

Hemoglobin, g/dL	14.3 ± 1.6
Fasting glucose, mg/dL	175 ± 70.9
A1c, %	7.9 ± 1.9
Total cholesterol, mg/dL	182 ± 47.5
LDL-C, mg/dL	107 ± 37.6
HDL-C, mg/dL	44 ± 14.6
VLDL-C, mg/dL	32 ± 25.8
Triglycerides, mg/dL	207 ± 187
TSH, mg/dL	2.8 ± 2.1
Creatinine, mg/dL	0.92 ± 0.33
eGFR ml/min/1.73m^2	86 ± 18.1
C-reactive protein, mg/dL	0.47 ± 0.23
AST, U/L	22 ± 13.7
ALT, U/L	28 ± 22.1
Troponin T, ng/mL	1.4 ± 6.6

Values are presented as mean ± SD or n (%). Hypertension, defined as previous diagnosis or use of any antihypertensive medication; Dyslipidemia, defined by LDL-C > 160mg/dL, Triglycerides > 150mg/dL, HDL< 40 (female) or < 50mg/dL (male), or use of any lipid lowering drug (statins, fibrates, ezetimibe); CVD, cardiovascular disease (coronary heart disease, cerebrovascular disease or peripheral artery disease); CHD, coronary heart disease (previous ACS, revascularization or diagnosed coronary artery disease); ACS, acute coronary syndrome (unstable angina, myocardial infarction); CAD, coronary artery disease; PCI, percutaneous coronary intervention; CAGB, coronary artery bypass graft; PAD, peripheral artery disease (defined by previous limb amputation, revascularization or diagnosed peripheral artery stenosis); eGFR, estimated glomerular filtration rate using CKD-EPI equation; obese, defined by BMI > 30 kg/m^2; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; BMI, body mass index; ARB, angiotensin II receptor blocker; CBB, calcium channel blocker; ACEi, angiotensin converter enzyme inhibitor; Sglt2i, sodium-glucose cotransporter type 2 inhibitor; GLP1, glucagon-like peptide 1; CCA-IMTc, common carotid artery intima media thickness; carotid artery disease, defined by IMTc >p75 or plaque; DSMP, distal sensorimotor neuropathy defined by Michigan Protocol; CAC, coronary artery calcium; OCT, Optical coherence tomography; A1c, glycated hemoglobin; LDL, low density lipoprotein; HDL, high density lipoprotein; VLDL, very-low-density lipoprotein; TSH, thyroid stimulating hormone; proteinuria, defined as urine protein / creatine ratio > 0.2 mg/g or urinary albumin-creatinine ratio > 30 mg/g. US$ 1.00 = R$ 5,00.