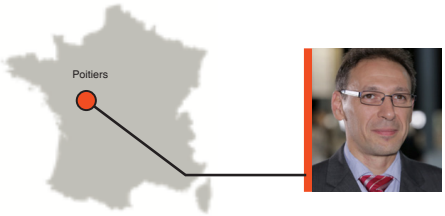
SURDIAGENE:
SURvival DIAbetes and GENEtics



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OVERVIEW

AT A GLANCE

> Diabetes and complications
> Type 2 diabetes (T2D)
> Coordinated by S. Hadjadj
> Poitiers University Hospital sponsorship
> Funded by PHRC, AFD, SFD, ANR
> Key words: Type 2 diabetes, complications, myocardial infarction, end-stage renal disease, heart failure, stroke

KEY FACTS & FIGURES

> Recruitment completed ; on-going follow-up
> 1,468 included patients in 2011 (25-75 yo)
> Follow-up mean: 6.3 years
> Monocentric cohort (Poitiers, France)
> Biobank: blood and urine collected at baseline

The aim is to study the genetic and environmental determinants associated with long-term complications of type 2 diabetes such cardiovascular disease including ischemic heart disease and severe heart failure, stroke and lower limb amputation, and severe renal outcomes and death.

Positioning

> Established collaboration with following projects: DIABHYCAR (France), ZODIAC (Netherlands) & ESTHER (Germany)

> The only type 2 diabetes complication-centered cohort in France

> The cohort is involved in the Innovative Medicines Initiative (IMI) 2 call which is Europe's largest public-private initiative

> Collaborations with EKF & Thermo Fisher companies (Diagnostic) are already on-going

LEADERSHIP

Prof. Samy Hadjadj, Professor in Endocrinology and Diabetology, Poitiers University Hospitals

Principal investigator of:

> The DIAB2NEPHROGENE study, a multicenter observational study on 2,000 patients with diabetic nephropathy aiming to explore the contribution of genes and environment to type 2 diabetes complication phenotypes

> The multicenter RADIAN trial, a randomized, placebo-controlled pilot trial aiming to test the protector role of raloxifene against urinary albumin excretion in post-menopausal women with type 2 diabetes

Coordinator of:

> The Genesis France-Belgium Study, a multicenter binational study designed to investigate the genetic factors involved in the microvascular complications of type 1 diabetes using a family-based design

> The biological resource center of Poitiers University Hospital (Poitiers biobanking facility)

Network

> Secretary of the EDNSG (European Diabetic Nephropathy Study Group) between 2009 and 2012. The EDNSG is a study group of the European Association for the Study of Diabetes (EASD) with special interest in diabetic nephropathy dedicated to study epidemiology, pathology, pathophysiology and treatment of this complication of diabetes mellitus

> General secretary of the French-speaking Society of Diabetology (SFD) since 2013

Stéphanie Ragot, PharmD., M.D. Ph.D., Methodologist

Associate Professor in Epidemiology and Public Health at Poitiers University

Coordinator of the master "Essais cliniques et développement du Médicament" at Poitiers University

Methodologist in Pluridisciplinary Clinical Investigation Center n°1402

Expert in clinical trial methodology and cardiovascular epidemiology

Member of the French Hypertension Society

SCIENTIFIC NETWORK & MANAGEMENT

Prof. S. Hadjadj works closely with European teams and is already engaged in a process for a collaboration with other cohorts such as:

> Brno Diabetes Cohort T1 & T2 a longitudinal study conducted in Brno, Czech Republic, assessing siabetic nephropathy in 450 diabetes patients and coordinated by K Kankova

> ESTHER Cohort, a cohort study conducted in Saarland, Germany, assessing chances of prevention and early detection of various chronic diseases including cancer among older adults. ESTHER is a population-based longitudinal study including about 10,000 elder adults coordinated by H Brenner/B Schottker

> Zwolle Outpatient Diabetes project Integrating Available Care (ZODIAC) study, a prospective observational cohort study of 1,300 diabetes patients coordinated by N Kleefstra

> DIABHYCAR, French participants of this RCT (low-dose ramipril *vs* placebo) are followed for 4 years and data are available for 3,137 subjects with T2DM and micro/macroalbuminuria. This study is coordinated by M Marre/ R Roussel

Prof. S. Hadjadj is also implicated in the Innovative Medicines Initiative (IMI-2) call: a project dedicated to biomarker in diabetic kidney disease in collaboration with M Marre (Paris) has been submitted

Through its collaborative projects and boards, SURDIAGENE implicates several experts in:

> **Endocrinology/Diabetology:** M Marre (Paris), R Roussel (Paris), V Rigalleau (Bordeaux)

> **Epidemiology:** V Migeot (Poitiers)

> **Biostatistic:** DA Tregouet (Paris)

> **Ethical and legal issues:** R Robert (Poitiers)

> **Cardiology:** D Montaigne (Lille), G Ducrocq (Paris), P Sosner (Paris)

> **Nephrology:** JM Halimi (Tours), Ph Zaoui (Grenoble)

PROJECT DESCRIPTION

SCIENTIFIC OBJECTIVES

- The SURDIAGENE study is based on an inception prospective monocentric cohort and aims to identify the **genetic** and **environmental determinants** of **microvascular and macrovascular complications in type 2 diabetes**
- Secondary objectives include investigation of the genetic determinants associated with **changes in urinary albumin excretion 2 and with other degenerative complications of diabetes (retinopathy, cardiovascular events)**

INNOVATIVE SCIENTIFIC FEATURES

- SURDIAGENE is derived from an hospital-based recruitment, associated with the **Poitiers Clinical Investigation Center** n°1402, taking advantage of the **hospital environment** for electronic health record, laboratory findings (allowing trajectory analysis), nutritional evaluations, cardiac ultrasound, etc.
- The cohort is designed to address the questions of diabetes complications and their genetic and environmental determinants, as a primary endpoint, allowing rapid publications, dedicated to type 2 diabetes and to diabetes complications

METHODOLOGY QUALITY

- Data quality assurance: high quality control, data scrubbing to ensure reliability and effectiveness of data collection
- Security procedures: mySQL database, on double-core server (Poitiers University Hospital Center)
- Certification: adjudication procedure for all endpoints (8 independent committee members reviewing all supporting documentation - Chairman Prof JM Halimi, Tours)

DESIGN, METHODOLOGY & TIMELINE

Recruitment objectives:	1,468 included patients – Poitiers University Hospital (Vienne, France)
Inclusion criteria:	Type 2 diabetes (T2D) – clinically defined Living in the Poitiers region
Exclusion criteria:	Non diabetic renal disease Fulfilling legal exclusion criteria (amended law dated on 20th December 1988)
End of follow-up:	Death Move out of the Poitiers region

INCLUSION COLLECTION
Baseline Data:
Clinical data: blood pressure, height, weight, CV history, parental history of diabetes, retinal status
Biological data: HbA1c, serum creatinine, urinary albumin to creatinine ratio (ACR), NT pro BNP, lipids
ECG
Treatments: at baseline with special emphasis on insulin and RAS blockers

FOLLOW-UP:
Database Updated every 2 years (since 2007): At each clinical patient examination: clinical measures (body weight, blood pressure) and key biological variables including serum, HbA1c, ACR & creatinine
Adjudicated endpoints: living status (cause of death), CV events (myocardial infarction, stroke, major amputation, severe congestive heart failure, artery revascularisation), renal events (renal replacement therapy, GFR trajectory), ophthalmological complications, cancer occurrence

DATABASE & BIOBANK CONTENTS

DATABASE

Demographic: Date of birth, ethnicity, gender, history of cardiovascular disease, BMI, height, on-going treatment

Comorbidities

> Active smoking, blood pressure, diabetes history with year of definitive insulin
> Renal function is based on a measurement of plasma creatinine and estimated glomerular filtration rate (GFR estimated by M.D.RD and CKD-EPI equations)
> Diabetic renal insufficiency (initial and during follow-up) is equally characterized by renal replacement therapy
> Glycemic control is evaluated by measuring glycated haemoglobin (HbA1c)
> Diabetic retinopathy stage is assessed by ophthalmogical record and/or retinography

Distant secondary clinical evaluation

Related to other databases: PMSI (Program for medicalization of the information systems), nutrition assessments, routine biological determinations & CepiDC (an national automated system for coding of causes of death, sponsored by Inserm)

Imagery data

> Routinely performed (no core center) echo-cardiocardiography
> Ejection Fraction ; Left ventricular mass ; E/A ratio

Key outcomes adjudicated by an independent committee

BIOBANK

Originality

> Availability of serum, plasma, DNA & urines for all patients at baseline

Scientific objectives

> Identification of genetic markers involved in type 2 diabetes development
> Identification of predictive and prognostic biomarkers from urine and blood samples
> Biobank is already involved in a IMI2 call and in the DIAGRAM (DIAbetes Genetics Replication And Meta-analysis) consortium aiming at performing large-scale studies to characterize the genetic basis of type 2 diabetes
> SURDIAGENE biobank is also implicated in the BIOBANQUES, a French biobanking network

Samples

> Blood sample, second morning urine & DNA

Associated resources

> SURDIAGENE biobank works closely with a platform comprising 2 experienced bio-technicians working with available hospital facilities for additional requirements

TECHNICAL MODALITIES & SPECIFICATIONS

ORGANIZATION

- The biobank is located at Poitiers BRC
- Each biological sample is identified by a patient-specific barcode

SPECIFICATIONS

- Date of the first sampling: January 2002
- Sampling frequency: at baseline for 1,468 patients and resampling during the follow-up for 476 patients through the metabolic disease biobank constitution
- Responsible for the biobank: Prof. S Hadjadj
- Protocol for the biological sample collection available
- A minimum data associated to each sample may be available on request
- Label of quality: Poitiers BRC has been AFNOR certified, according to French biological research center standard NF S 96-900. Biobank procedures have been developed by the Biological Resource Center in order to apply standardized methods for sample collection, treatment and conservation (Standard Operating Procedure)
- Biological samples are already available

BIOLOGICAL SAMPLE COLLECTION & ACCESS

Biological specimens	Origin	Quantity / concentration available	No. of aliquot	No. of sampled patients	Storage conditions
At baseline (date of the first sampling): January 3rd, 2002					
Serum	Blood	200 µl	3	1,468	-80°c
Serum	Blood	1 ml	1	1,468	-80°c
Plasma EDTA	Blood	500 µl	3	1,468	-80°c
Plasma EDTA	Blood	1 ml	2	1,468	-80°c
Heparin serum	Blood	500 µl	3	1,468	-80°c
Heparin serum	Blood	1 ml	2	1,468	-80°c
Urines	Second morning urine	500 µl	4	1,468	-80°c
Urines	Second morning urine	2 ml	2	1,468	-80°c
DNA	Blood	300 µl	2	1,468	-80°c
Heparin serum	Blood	500 µl	3	1,468	-80°c
During the follow-up: first sampling during the follow-up June 2nd, 2010					
Plasma EDTA	Blood	1 ml	2	18	-80°c
Heparin serum	Blood	1 ml	2	476	-80°c
Serum	Blood	1 ml	2	476	
Urines	Second morning urine	1,6 ml	2	476	-80°c
DNA	Blood	100 µl	1	476	-80°c
Plasma EDTA	Blood	1 ml	2	18	-80°c
Heparin serum	Blood	1 ml	2	476	-80°c
Serum	Blood	1 ml	2	476	
Urines	Second morning urine	1,6 ml	2	476	-80°c

BIOBANK SAMPLE ACCESS MODALITIES

- Biological samples will be accessible to public and/or private/industrial teams after scientific committee approval on a basis of a scientific project
- Major biological samples are accessible to public and private research teams. Limited access to samples of dead patients or to patients without resampling will be applied due to restricted material quantity
- To access to the biological resources, a specific template has to be filled. This template is available online
- Biological samples can be transferred to public or private teams, including foreign companies, according to modalities defined in a contract

BIOLOGICAL SAMPLE ANALYSES

- The SURDIAGENE cohort already exploits the biological samples in following projects:
  - > EKF Diagnostics, the global diagnostics company, has used the SURDIAGENE cohort to show that TNF Receptors 1 and 2 are strong biomarkers of progressive Diabetic Kidney Disease (DKD) and validate its diagnostic test
  - > Establishment of a genetic risk score of rapid decline renal function in patients with type 2 diabetes
  - > Biomarker identification approach for all-cause and cardiovascular deaths, beyond clinical covariates
  - > Biomarker identification approach for major adverse cardiac events and renal outcomes, beyond clinical covariates
- Biological sample analysis-derived data will be accessible to public and private/industrial teams after evaluation of scientific projects

COST

- A financial estimation of the biobank constitution is available
- A price list regarding the cost of each biological sample is already established and available on request

RESEARCH COLLABORATION OPPORTUNITIES

Phase IV Product approval Phase III Phase II Phase I Pre-clinical Proof of concept

Translational research

> **Identification of biomarkers** for the development of diagnostic or prognostic tests based on the correlation of biological and clinical data: inflammation-related biomarkers, natriuretic peptides, oxidative stress biomarkers

> **Cardiovascular prognosis** in patients with type 2 diabetes

> **Pathophysiology studies**

> Description of the influence of sex on **renal function** decline in type 2 diabetes – trajectory approach

> **Mendelian randomisation** for BP and CV and renal outcomes (Association between gene polymorphisms including Genetic risk score and BP/MACE and renal outcomes)

Clinical development

> Validation of biomarkers to define clinical stages and improve therapeutic guidance

> **Design of clinical trial** before companion test development

> Assessment of the cardiovascular prognostic values of different criteria for various cardiovascular endpoints in T2D patients

> Assessment of the **prognostic value of serum marker** for all-cause death in T2D and diabetic kidney disease (DKD)

> Optimization of clinical studies with development of **interactive tool for eGFR trajectory** assessment

> Support clinical enrollment: **rapid renal function decliner** identification for RCT design

> Development of clinical score for **severe congestive heart failure** in T2D patients

Outcomes research

> Pharmaco-epidemiological studies:
>> Prescription detailed at baseline
>> PMSI details for 1,230 subjects with at least one hospital-stay during follow-up

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