UNIL | Université de Lausanne
Faculté de biologie
et de médecine

Mémoire de Maîtrise en médecine No 3644

Analysis of a Lausanne cohort of patients with diabetic nephropathy and comparison with European cohorts

Student
Vehashini Sabaratnam

Tuteur
PD Dr Anne Zanchi
Service de Néphrologie et Diabétologie

Expert
Prof. Michel Burnier
Service de Néphrologie

Lausanne, December 2016

1 Table of contents

Abbreviation:

↑	Mortality
ABI :	ankle brachial index
ACEi :	angiotensin-converting enzyme inhibitor
ACR :	albumin creatinine ratio
ADA :	American Diabetes Association
ADMA :	asymmetric dimethyl-arginin
Aix :	augmentation index
ARF :	acute renal function
CHD :	coronary heart disease
CV:	cardiovascular
CVD :	cardiovascular disease
DN:	diabetic nephropathy
DR :	diabetic retinopathy
DRIN :	dynamic renal resistive index
EH :	hypertension group
EPC :	elevated plasma creatinine
FPG:	fasting plasma glucose
Glc :	glucose
hs-CRP :	high sensitive CRP
HT :	hypertension
IMT :	intima media thickness
MaA :	macroalbuminuria
Mi :	myocardial infarctus
MiA :	microalbuminuria
MMP :	matrix metalloproteinases
NA :	normal albuminuria
NFR1 :	Nod Factor Receptor 1
NPHS2 :	podocin
OAD :	oral antidiabetic drug
p-FGF23 :	Fibroblast growth factor 23
PCC :	plasma creatinine concentration
Pts :	patients
RFD :	renal function decline
RKF :	reduced kidney function
RRF :	reduced renal function
RRT :	renal replacement therapy
SBP:	systolic blood pressure
SMDA :	symmetric dimethyl-arginin
T1D :	type 1 diabetes
T2D :	type 2 diabetes
TNFR1 :	tumor necrosis factor receptor
Ttt :	treatment
u-NGAL:	urinary - Neutrophil Gelatinase-Associated Lipocalin
UAC :	urine albumin concentration
UAE:	urine albumin excretion
uGpnmb :	urinary-glycoprotein non-metastatic melanoma B
uKIM1 :	urinary-Kidney Injury Molecule 1
Y :	years
YKL-40 :	chitinase 3-like 1

Part 1

2 Objective of this master thesis

The goal of this Master thesis is to list the prospective European cohort studies and to compare them to SWIDINEP (Swiss diabetic nephropathy cohort), a prospective cohort study on diabetic nephropathy currently underway in Lausanne.

3 Diabetic nephropathy /diabetic kidney disease (DKD)

3.1 Definition of diabetic nephropathy (DN)

Diabetes is the major cause of chronic kidney disease throughout the world and the first cause of end-stage renal disease.

Diabetic nephropathy is defined by the presence of macroalbuminuria (albumin excretion > 300mg/24h or albumin/creatinine ratio >30mg/mmol (>300mg/g)) and/or an alteration of creatinine clearance (GFR<60ml/min/1.73m2) (5).

The screening of DN is based on annual assessments of kidney function, by estimating GFR (eGFR) with creatinine-based equation (MDRD, CKD-EPI) and measuring the albumin/creatinine ratio (6). These measures are used for clinical staging of DN according to the KDIGO 2012 classification (Table 1) which will classify the patients by low, medium and high renal and cardiovascular risks.

CKD Classification and Staging

Green: Low risk (LR)
Yellow: Moderate risk (MR)
Orange: High risk (HR)
Red: Very high risk (VHR)

Kidney function stage GFR (ml/min/1.73m²) Description and range				Kidney damage stage Urine albumin/creatinine ratio Description and range		
				A1	A2	A3
				Normal to mild increase <30mg/g	Moderate increase 30-300 mg/g	Severe increase >300mg/g
	G1	Normal or high	≥90	LR	MR	HR
	G2	Mild decrease	60-89	LR	MR	HR
	G3a	Mild to moderate decrease	45-59	MR	HR	VHR
	G3b	Moderate to severe decrease	30-44	HR	VHR	VHR
	G4	Severe decrease	15-29	VHR	VHR	VHR
	G5	Kidney failure	<15	VHR	VHR	VHR

Table 1. CKD Classification and Staging
Source: http://www.lovekidneys.com/providers/treatment.php

Despite the strength of albuminuria as a risk biomarker for DN and CVD outcomes, a few major limitations should be considered. Albuminuria levels have a large variability with a large proportion of patients regressing from microalbuminuria to normoalbuminuria. Furthermore, around 30% of patients with DN have a decline in renal function without albuminuria. Some studies suggest that the decline in eGFR is slower in type 2 diabetic patients with a low or a normal albuminuria (6).

It is also important to know that eGFR has at best a 90% chance of being within 30% of measured GFR. Moreover, the characteristics of the GFR estimating equations make them significantly less precise at higher GFRs. This is a main concern for the early stage of DN, as it is associated with a high GFR (hyperfiltration) followed by an accelerated renal function decline (6).

These limitations should be kept in consideration while reading or analysing studies.

3.2 Pathogenesis of diabetic nephropathy

The exact pathogenesis of diabetic nephropathy is complex and is not, for now, completely understood. It involves metabolic, hemodynamic and inflammatory pathways (Figure 2). Risk factors include hyperglycaemia, increased activity of the renin-angiotension-aldosterone system (RAAS) and an increased intraglomerular and systemic blood pressure (7).

Hyperglycemia can result in renal damage if the exposure is longstanding. In such case, it causes renal damage due to metabolic effects as well as direct hemodynamic effects with glomerular hypertension and subsequent hyperfiltration (7). All these mechanisms lead to the development of glomerulosclerosis, which participates in the reduced kidney function.

Furthermore, epidemiological and familial studies have shown that genetic susceptibility can contribute to the development of diabetic nephropathy in patients with both type 1 and 2 diabetes (8). The importance of genetics for this disease has become a focus of research for ongoing studies with the hope of identifying genetic markers of diabetic nephropathy.

Figure 2 illustrates the major pathways and the molecular mediators in the pathophysiology of diabetic nephropathy (9).

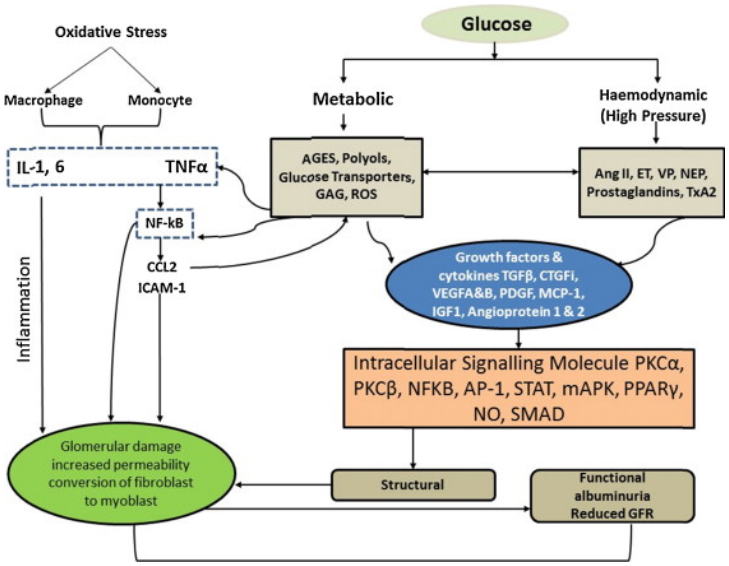

Figure 1 Major pathways and molecular mediators in the pathophysiology of diabetic nephropathy.

Abbreviations: IL-1, 6, interleukin 1, 6; TNF-α, tumour necrosis factor α, NF-kB, nuclear factor kB; CCL2, chemokine (cc-motif) ligand 2, also called monocyte chemotactic protein 1 (MCP-1); ICAM-1, intercellular cell adhesion molecule 1; PKC, protein kinase C; AGEs, advanced glycation end products; AP-1, activator protein 1; CTGF, connective tissue growth factor; MAPK, mitogen-activated protein kinases; MCP-1, monocyte chemoattractant protein 1; NEP, neutral endopeptidases; NO, nitric oxide; PAI-1, plasminogen activator inhibitor 1; PDGF, platelet derived growth factor; PPARG, peroxisome proliferating activated receptor gamma; ROS, reactive oxygen species; STAT, signal transducer and activators of transcription; TGF-β, transforming growth factor beta; TXA, thromboxane; VEGF, vascular endothelial growth factor; VP, vasopressine.

Source : Ahmad J. Management of diabetic nephropathy: Recent progress and future perspective. Diabetes Metab Syndr Clin Res Rev [Internet]. 2015 Mar [cited 2015 Sep 26]; Available fro
m: http://linkinghub.elsevier.com/retrieve/pii/S1871402115000211

3.3 Epidemiology and management of diabetic nephropathy

Around 30% of diabetic patients will develop some degree of nephropathy. Diabetic nephropathy is the leading cause of end-stage renal disease (ESRD), representing approximately 50% of ESRD cases in the developed world. A recent study in the Canton de Vaud identified that 47% of all patients on renal replacement therapy (hemodialysis or peritoneal dialysis) had diabetes as a co-morbidity (personal communication). Even if the incidence rate for ESRD attributed to DN has stabilized in the recent years, these rates continue to rise in high-risk groups, such as middle-aged African Americans, Native Americans and Hispanics (6).

DN represents a high cost of care for people with diabetes. It is largely due to the strong relationship between DN and both cardiovascular disease (CVD) and the development of ESRD.

Consequently, it is also important to discuss the cardiovascular risks of DN. Among patients with diabetes, those with kidney disease are described as having a high rate of mortality (6). This increase is mainly due to CVD. Albuminuria and eGFR are independently and additively associated with increased risks of CVD events, CVD mortality, and all-cause mortality.

All these facts should be considered in general practice when we diagnose diabetic patients and in their follow-up.

The recommendation for the follow-up of diabetic patients is managed by the American Diabetes Association (ADA). Their goal is to provide clinicians, patients, researchers, financial contributors and other interested individuals with the components of diabetes care, general treatment goals, and tools to evaluate the quality of care (10).

In 2014, diabetologists and nephrologists met to discuss diabetic nephropathy and published the ADA consensus conference report (10).

The major topics discussed in the ADA consensus conference report were as follows:

I. *Identification and monitoring cardiovascular disease and management of dyslipidemia, hypertension*
II. *Use of renin-angiotensin-aldosterone system blockade and mineralocorticoid receptor blockade,*
III. *Glycemia measurement, hypoglycemia, and drug therapies,*
IV. *Nutrition and general care in advanced-stage chronic kidney disease,*
V. *Children and adolescents*
VI. *Multidisciplinary approaches and medical home models for health care delivery.*

The main question raised in the report was: “Can algorithms be developed to predict risk for progressive DN, and which factors must be incorporated?”

Thus, there is a need for prospective cohort studies of diabetic nephropathy to identify new markers of diabetic nephropathy.

4 Listing of European cohorts on diabetic nephropathy: Methods

4.1 Aim

We chose to focus our search on **prospective observational non-interventional studies** of **diabetic subjects** in **European countries**. The studied population was comprised of patients with **type 1 and type 2 diabetes**. We narrowed down our literature review to **articles published during the past ten years in Europe,** which examined **renal parameters and markers of renal function decline.**

4.2 Definition of a cohort (1)

In a cohort study, subjects are followed over time to describe the incidence or the natural history of a condition and to analyse predictors for various outcomes. Measuring a predictor before the outcome establishes the sequence of events and helps to control bias.

4.3 Definition of a prospective cohort

In a prospective cohort study, the investigator begins by assembling a sample of subjects. The investigator measures each subject's characteristics that might predict the subsequent outcomes, and follows these subjects with periodic measurements of the outcomes of interest for a determined time.

Strengths (1):

- powerful strategy for assessing incidence
- measures the levels of the predictor before the outcome occurs and establishes the time sequence of outcomes
- prevents the predictor from being influenced by knowledge of the outcome
- measures variables in a more accurate way than in a retrospective study[1]
- become more efficient as the outcomes become more common and immediate

Weaknesses (1) :

- large induced costs and inefficiency in the study of rare outcomes
- for rare outcomes, a large number of people must be followed for a long period of time to observe sufficient outcomes to produce meaningful results

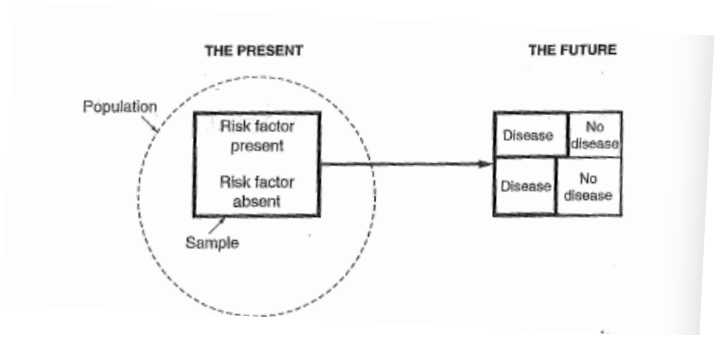

Figure 2 Prospective cohort study explained graphically

[1] In a retrospective study, the investigator choses a cohort that has already been assembled, has baseline measurements and a follow-up.

We also have to make a distinction between the observational and the interventional prospective cohort. In an observational cohort, no intervention is carried out by the investigator; they have only to observe whether the subjects develop the outcome of interest.

In an interventional prospective study, one group will be exposed to or treated with the agent of interest, whereas the other group will not, thus acting as a control group. (2)

4.4 Definition of a registry

A patient registry is an organized system that uses only observation study methods to collect uniform data (clinical and other). The patients are enrolled on the basis of either disease or exposure status, by the physician who decides how the patient is to be treated. It helps in evaluating specified outcomes for a population defined by a particular disease, condition or exposure (3).

It can be used to construct a cohort, to produce a sample for a cross-sectional study, or to identify people with certain conditions or outcomes.

It differs from a cohort in that registry studies are observational and cohort studies are investigational. In a registry study, the physicians decide how to treat the condition and hence are passive observers; in a clinical study, they instruct the investigator to treat or investigate the condition in a certain manner, and in that way act as active researchers (4).

4.5 Renal criteria for the literature research

4.5.1 First method

For the literature study, we used the **Pubmed platform**. We limited our research to studies **published within the last 10 years**, carried out in European countries and written in English.

Diabetic nephropathy is a large topic on which numerous articles have been published. When we started our study, we had to reduce our results using pertinent keywords and filters on Pubmed.

1. The question used on **Pubmed using MeSH database** was as follows:

"Kidney Diseases/epidemiology"[Majr] AND ("Diabetes Mellitus, Type 1"[Majr] OR "Diabetes Mellitus, Type 2"[Majr])) AND "last 10 years"[PDat] AND English[lang])) AND "country"[tiab]) AND "last 10 years"[PDat] AND English[lang]).

We consulted with this question and changed the country each time, using the following countries: *France, Italy, Austria, Spain, Portugal, Belgium, Netherlands, United Kingdom (UK), Ireland, Denmark, Germany, Norway, Sweden, Finland, Poland and Romania.*

Out of the 40 articles found, only **9 were relevant**. We removed those relating studies conducted in the USA, Canada or Australia. Others were not relevant to our objective or, being too short and insignificant, could not be used for our analysis.

Other studies were retrospective, cross-sectional or interventional, and thus could not be included in our research.

4.5.2 Second method

A second survey was conducted **using concept key words**, to include articles which were at the time **not indexed in Medline with MeSH terms**.

We needed to create concepts using key words and then combine them.

The four key word concepts were:

- **Concept 1** : "diabetes mellitus"[Majr] OR "diabetic Nephropath*"[Majr] (diabetes AND (Type 1 OR Type 2)) OR “Diabetic Glomerulosclerosis” [tiab] OR “Adult-Onset Diabetes Mellitus” [tiab]
- **Concept 2** : "Kidney Diseases "[Majr] OR “Albuminuria” [tiab]
- **Concept 3** : Europe[tiab] OR France[tiab] OR Germany[tiab] OR England[tiab] OR "Great Britain"[tiab] OR Finland[tiab] OR Spain[tiab] OR Italy[tiab] OR Sweden[tiab] OR Norway[tiab] OR Netherland*[tiab] OR Italy [tiab] OR Austria [tiab] OR Ireland [tiab] OR Denmark [tiab]
- **Concept 4:** “Prospective study” [tiab] OR “observational study” [tiab]

We formulated questions using these 4 concepts:

"diabetes mellitus"[Majr] OR "diabetic Nephropath"[Majr] OR (diabetes AND (Type 1 OR Type 2) [Majr]) OR Biological markers [tiab])) AND ("Kidney Diseases/epidemiology"[Majr] OR "Kidney Disease*"[Majr] OR Albuminuria [tiab] OR Risk Factors)) AND (Europe[Majr] OR France[tiab] OR Germany[tiab] OR England[tiab] OR "Great Britain"[tiab] OR Finland[tiab] OR Spain[tiab] OR Italy[tiab] OR Sweden[tiab] OR Norway[tiab] OR Netherland*[tiab] OR Italy [tiab] OR Austria [tiab] OR Ireland [tiab] OR Denmark [tiab])) AND (Prospective study [tiab] OR observational study [tiab])”*

As a result, 55 articles came up, of which only **5 corresponded** to our research. As in the first study, the excluded articles were either retrospective, cross-sectional or were not conducted in Europe.

4.5.3 Third method

Halfway through the study, we came to realise that the two first reviews of the literature were not sufficiently thorough. As a consequence, we came up with a new strategy including new keywords and different combinations. The following table contains the new keywords.

Retained concept / Vocabulary	**Population** Diabetic Nephropathy	**Intervention** Progression	**Comparison** Biomarkers
Keywords	Diabetic Nephropath*[tiab] Diabetic kidney disease*[tiab]	Disease progression*[tiab] disease development*[tiab] disease evolution[tiab] Disease course[tiab]	Biomarker*[tiab] Biological marker*[tiab] Bioindicator*[tiab] Marker*[tiab]
MeSH	"Diabetic Nephropathies"[Mesh]	"Disease progression"[Mesh]	"Biomarkers"[Mesh]

Table 2. Study questions on the Pubmed database

With the help of this table, we created a new question on the Pubmed database:

("Biomarkers"[Mesh] OR Biomarker[tiab] OR Biological marker*[tiab] OR Bioindicator*[tiab] OR Marker*[tiab]) AND ("Disease progression"[Mesh] OR Disease progression*[tia b] OR disease development*[tiab] OR disease evolution[tiab] OR Disease course[tiab]) AND ("Diabetic Nephropathies"[Mesh] OR Diabetic Nephropath*[tiab] OR Diabetic kidney disease*[tiab])*

A total of 312 articles came up based on the filter of **10 years** and we selected **English-written** articles only. As a result **13 new articles** were selected. Those we excluded were either conducted outside of Europe, were cross-sectional or did not correspond to our objective.

4.5.4 Fourth method

We also chose to do a study on another database called **Embase** that contains articles not indexed on Medline.

The research question on this database was:

(('diabetic nephropathy'/de OR (Diabetic NEAR/3 Nephropath):ab,ti OR ((Diabetic NEAR/5 kidney):ab,ti AND disease:ab,ti)) AND ('disease course'/de OR (disease NEAR/3 progression):ab,ti) AND ('biological marker'/de)) AND ('cohort analysis'/de OR 'comparative study'/de OR 'longitudinal study'/de OR 'observational study'/de OR 'prospective study'/de)*

This resulted in 31 articles, of which **only 2 were relevant**.

We should mention that few articles were found by corresponding studies. When a prospective study was found, all the published articles of the ongoing cohort were kept.

4.6 Vascular criteria for the literature research

We also had to carry out a literature research for cohort studies in diabetic nephropathy with vascular endpoints. In the SWIDINEP cohort, patients are extensively characterised at the vascular level (pulse wave velocity, carotid intima-media thickness, renal vascular resistance, 24h blood pressure measurements).

In order to obtain a rough comparison, we had to look up for European studies exploring this subject.

For the study, we used the following keywords:

Pulse way velocity ; Intima media thickness ; Sphygmor ; Renal volum ; Renal resistance index ; diabetic nephropathy ; diabetic kidney disease ; type 1 diabetic ; type 2 diabetic ; Europe ; prospective

We found **in total eleven articles concerning studies conducted in Europe**: two prospective studies and eight cross-sectional studies with vascular markers in patients with DN and one prospective study conducted in Rotterdam with subjects who were not necessarily diabetic. This study was not found with these keywords.

4.7 Results

4.7.1 Renal criteria studies

After these four different literature searches, we had **31 original publications in total**. We decided to create two tables. One (Table 4) lists the cohort studies and the other (Table 3) the studies based on a registry. We classified them by year of publication, first author, country, cohort name, number of subjects, median follow up, inclusion and exclusion criteria, objective of the study, renal endpoints (surrogate markers), hard endpoints and finally by results. Both tables provided a good overview of the latest studies conducted on diabetic nephropathy and its progression.

Table 3. Registry studies

Ref	First author	Country	Name of the registry	Number of subjects	Median follow up (years)	Inclusion criteria	Exclusion criteria	Objective	*Renal/Vascular Endpoints*		Results
									Surrogate markers	*Hards endpoints*	
25	FINNE et al. 2005	Finland	Finnish Diabetes Register (≠ Finndiane)	20005	16.7	**T1D** ; <30y	T2D; ESRD at baseline	Estimate the long-term risk of developing ESRD. Assess how age at dg of diabetes, time period of dg and sex affect the risk	none	ESRD ; †	Cumultative incidence of ESRD was 2.2% at 20y and 7.8% at 30y after dg ; Lower risk for ESRD if diagnosed <5y , no differencce between sexes.
26	SVENSSON et al. 2013	Sweden	Swedish National Diabetes Register	66065	5.7	**T2D**; 30-79y	BMI <18.5 and > 45 kg/m2 ; eGFR < 30mL/min/1.73 m2	Investigate the RRF & albuminuria prediction of CV events & † in T2D. Role of co-existing congestive heart failure & other CV risk factors on CV events	Renal impairment eGFR <60 mL/min/1.73 m2	fatal or non-fatal CHD/CVD; †	Increasing levels of albuminuria & renal impairment were independently associated with increasing risk of CV events and all cause †.In NA pts, a reduced renal function is an important predictor of CV events and of all cause †.Glycemic control, smoking & hyperlipidaemia had important effects on risk for CV events in pts with albuminuria.
27	NAG et al. 2007	UK	data from South Tees diabetes mortality Study	3288	10.6	**T1D; T2D**		Find an association between eGFR and all-cause and cardiovascular †	eGFR ; conventional CV risk factors	CV †	Total and cardiovascular † increased with reduced eGFR.
28	BRUNO et al. 2009	Italy	Registry of Province of Turin	1210	15.8	**T1D;** 0-29y	-	Estimate short-term † in the cohort with disease onset in the period 1974-2000. Assess differences in † risk between childhood (0-14y) and young adult - onset (15-29y) T1D	none	†	Early † in a cohort of children and young adults with T1D is two-fold higher than the control population. Risk of † is higher in adulthood than in childhood-onset diabetes.

Table 4. Prospective cohort studies

Ref	First author	Country	Name of the cohort	Number of subjects	Median follow up (y)	Inclusion criteria	Objective	Renal Endpoints	-	Results	Biobank
								Surrogate markers	*Hard endpoint*		
38	RETNAKARAN et al.2006	UK	UKPDS 74	5102	15	newly diagnosed **T2D** ; 25-65y, without albuminuria or with normal plasma creatinine at baseline	Identify risk factors of diabetic nephropathy	MiA or MaA; reduced creatinine clearance, doubling of plasma creatinine	ESRD ; RT ; †	38% developed albuminuria and 29% renal impairment. Risk factors were systolic blood pressure, high urinary albumin excretion, high plasma creatinine and Indian-Asian ethnicity.	**Yes (genetics)**
66	CONWAY et al.2012	UK	ET2DS	978	4	**T2D** ; 60-75y	Evaluate **u-KIM1 and Gpnmb** as markers of progression/regression of MiA	MiA to MaA		Higher uKIM-1/Cr and uGpnmb/Cr ratios were associated with a faster decline in renal function on univariate analysis but not following adjustment for known risk factors, as baseline ACR, HbA1c, systolic blood pressure and eGFR.	No
40	LOOKER et al. 2015	Scotland	GO-DARTS	307	3.5	**T2D;** CKD stage 3.	Identify markers of RFD	eGFR		12.5% with CKD3 had a loss of >40% of eGFR (=cases). Cases had longer diabetes duration, greater prevalence of albuminuria and retinopathy and lower eGFR at baseline than controls. Identification of 14 biomarkers that contained predictive information beyond clinical covariates, as beta2-microglobulin, cystatin C, FGF-21, uracil, strongest predictor was SDMA/ADMA.	**Yes (genectics)**
16	SCHÖTTKER et al. 2013	Germany	ESTHER Study	3538	8	Prediabetes ; 50-74y	Identify risk factors of rapid renal function decline in prediabetes	Rapid kidney function decline (average annual eGFR decline of at least 3 mL/min/1.73 m2)	†	RKF higher in subjects with pre-diabetes but after adjusting for established CV risk did not persist. In diabetes, RKF risk increased linearly with increasing FPG & HbA1c (>6.4%).	No
17	DÖRHÖFER et al. 2013	Germany	DIACORE	aim 6000	10	**T2D;** >18y	Identify novel mechanisms involved in the development and progression of DN	time to doubling serum creatinine ; time to incident RRT	† all cause	not published yet	**Yes (genetics)**
42	PENA et al. 2015	Netherlands	PREDICTIONS	82	4	**T2D,** 35-75y	Identify a novel panal of biomarkers predicting renal function decline in T2D	eGFR	-	Higher concentrations of the individual biomarkers MMP2, MMP7,YKL-40, NFR1,NPHS2 and endostatin were significantly associated with eGFR decline.	No
23	M. VAN DER VELDE et al.2011	Netherlands	PREVEND	8592	6.5	**T2D** or non-diabetic; 28-75 y	Investigate UAE and **high-sensitive CRP** in predicting new-onset T2D, CVD and CKD in addition to the present MetS defining criteria	new onset T2D ; new onset CKD (eGFR <60ml/min/1.73m2) ; new onset CVD	†	MetS and elevated UAE had a higher risk for the three outcomes. Subjects with MetS and high hs-CRP had higher incidence for CKD and CVD.	No
24	PENA et al. 2014	Denmark/Netherlands	Steno studies PREVEND	240	2.9	**T2D** ; HT	Investigate markers predicting micro- or MaA in pts with T2D or HT	UAE ; eGFR	-	In T2D, a significant correlation was found between metabolites (plasma and urine as butenoylcarnitine, histidine or urine glutamine) and progression of eGFR and UAE. In urine, glutamine was negatively correlated UAE and positively correlated with eGFR In T2D. Urinary tyrosine and urinary hexose were significantly lower in T2D micro- to macroalbuminuria cases.	No
18	NIELSEN et al. 2011	Denmark	-	177	3.5	**T2D;** 20-70y	Determine the role of **p-FGF23, u-NGAL and u-KIM1** as predictors of decline in eGFR in pts T2D and DN	MiA to MaA ; decline of eGFR	-	Pts with u-KIM1 in the highest quartile had a greater decline in eGFR.Higher levels of u-NGAL or u_KIM1 were associated with a faster decline in eGFR but neither predicted development from MiA to MaA .	No
19	ANDRESDÒTTIR et al. 2013	Denmark	-	72	4	**T1D** ; DN	Evaluate whether urinary sulphate excretion is associated with progression of DN in T1D pts	-	ESDR ; †	Urinary sulphate excretion was a significant determinant of GFR decline.	No
20	NORDWALL et al. 2015	Sweden	VISS Study	451	21.1	Newly dignosed **T1D** ; dg < 35y	Evaluate HbA1c as a predictor of severe microvascular complications. Formulate HbA1c target levels for ttt	MiA ; MaA	-	Keeping the average HbA1c below 7.6% seemed to be sufficient to prevent both persistent MaA and retinopathy for at least 20 y in T1D pts.	No
21	SVENSSON et al. 2015	Sweden	Diabetes Incidence Study in Sweden (DISS)	468	17	newly diagnosed diabetes **(T1D, T2D)**; 15-34y.	Identify risk factors of nephropathy in a population-based cohort	MiA or MaA	ESRD ; †	15% of all pts (T1D,T2D) developped DN after 17y.Pts with T2D diagnosed as young adults seem to have a increased risk of DN. Among DN patients, 91% had MiA & 8.6% MaA. Age at onset of diabetes, BMI and HbA1c but not SBP were significant predictors of developping DN.	No
22	Ole TORFFVIT 2012	Sweden		118	4	**T2D** ; with MiA or MaA; indication for renal biopsy	Examine if noctural BP has higher prognostic signifiance than daytime BP and office BP	GFR < 30 ml/min/1.73 m2 ; dialysis	†	Achieving the goal of <140mmHg (day and nighttime) lowered the risk of uremia. Only 55% of the patients reached the nighttime goal and 31% for the daytime. Reaching the goal for nighttime BP decreased risk for dialysis ttt.	No
29	PANDURU et al. 2015	Finland	FinnDiane	2090	5.8	**T1D**	Evaluate the predictive value of **urinary adiponectin (uADP)** for the progression of DN	Change in AER		uADP is a strong and independant predictor of DN progression to ESRD in patients with T1DM and was an even better predictor than AER and as good as eGFR.	**Yes (genetics)**
30	THORN et al. 2015	Finland	FinnDiane	3809	13	FinnDiane pts without ESDR (dialysis)	Investigate the prevalence and progonsis of NA CKD in T1D	CKD (eGFR <60 mL/min/1.73 m2). Albuminuria	ESDR ; †	At baseline, 2% were non-albuminuric. Factors independently associated with NA CKD: female, HDL cholesterol, absence of retinopathy, absence of HTAt. NA CKD increased CV morbidity and all cause mortality but not renal outcomes.	
31	WADEN et al. 2015	Finland	FinnDiane Study physical activity/diabetes type I	1390	6.4	**T1D**	Assess how physical activity predicts the developpement & progression of DN in T1D	Any shift to a higher albuminuria class	ESRD; †	The total amount of leisure-time physical activity (LTPA) was not associated with progression in renal status. The 10 year cumultative progression rate was 24% for low intensity ; 13,5% for moderate ; 13.1% for high intensity LTPA. Physical activity, in particular its intensity may have an impact on the initation and progression of DN in T1D.	

Table 4 continued from previous page

Ref	First author	Country	Name of the cohort	Number of subjects	Median follow up (y)	Inclusion criteria	Objective	Renal Endpoints	-	Results	Biobank
								Surrogate markers	*Hard endpoint*		
32	VAN DER KLOET et al. 2012	Finland	FinnDiane	52	6	**T1D**	Identify urinary biomarkers that differentiate the progressive from the non-progressive form of albuminuria (MiA or MaA)	serum creatinin ; AER		Discriminating metabolites included acyl-carnitine, acyl-glycines and metabolites related to tryptophan metabolism were associated with the progressive form of CKD.	**Yes (genetics)**
33	FORSBLOM et al. 2011	Finland	FinnDiane	592	9	**T1D;** MaA	Identify the predictors of the cumulative incidence of ESRD or pre ESRD	none	ESRD; †	Pts who developped ESRD had lower baseline renal function and worse blood glc, lipid, and BP control.	
34	GROOP et al. 2009	Finland	FinnDiane	4201	7	newly diagnosed **T1D** ; <35y	Identify clinical features associated with premature † in T1D	none	†	Excess † was only observed in pts with CKD. The increase † in across each stage of albuminuria was equal to the risk induced by preexisting macrovascular disease. GFR was independently associated with † .	
37	PENNO et al. 2013	Italy	RIACE	8260	1	**T2D**	Evaluate the association of HbA1c variability with microvascular complications	AER ; ACR ; eGFR <60ml/min/1.73m2	†	Higher variability (higher HbA1c-SD) was associated with younger age, shorter duration of diabetes. More MiA and MaA, reduced eGFR, stage CKD, advanced DR increased with the increasing variability of HbA1c. HbA1c variability affects CKD more than average HbA1c.	
11	PENNO et al.2012	Italy	RIACE	15 773	1	**T2D**	Examine the association between CKD and diabetic retinopathy			Concordance between DR and CKD was found in 11.5% of the subjects. Pts with CKD, alone or associated with DR were older, with higher TG and lower HDL. Albuminuria was higher in pts with advanced DR but eGFR did not differ between groups.	
12	PUGLIESE et al. 2011	Italy	RIACE	4062	1	**T2D**	Investigate the reproductibility of **UAE** in T2D			Concordance rate between a single UAE and the geometric mean of multiple measurements was 94.6% for NA, 83.5% for MiA and 91.1% for MaA. A single value of UAE is an accurate predictor of nephropathy stage.	No
64	PENNO et al. 2011	Italy	RIACE	15733	1	**T2D**	Evaluate the association of non-albuminuric T2D CKD patients with CV risk factors and other complications			52 % of the pts had NA. Of the 18% with eGFR <60, 56% were NA. NA CKD were more frequently female gender, non-smokers, had shorter diabetes duration and were less on antihypertensive ttt. Had Lower : HbA1c, levels TG, serum creatinine (higher eGFR). The prevalence of NA phenotype was higher in stage >3 CKD pts not on ACE ttt.	
13	FABBIAN et al. 2015	Italy	-	1284	4.5	**T2D**	Evaluate the relationship between complications and eGFR	eGFR <60 ml/min/1.73m2 ; CV † ; Non-fatal CV events; episode of CHF; cerebrovascular events	† ; RRT	Worse degree of renal impairment (<30-45 ml/min/1.73m2) were the major predictors of decreasing clinical conditions. All the others clinical parameters including patient history were not related to complication development.	No
14	ZOPPINI et al. 2012	Italy	Verona Diabetes Study	1682	10	**T2D**	Examine predictors of the annual decline in eGFR in T2D and preserved kidney function	eGFR decline	†	During follow-up,15.6% were rapid decliners (eGFR decline >4.0%7y).They were significantly older, had a longer duration of diabetes and were more likely to have HT, DR and albuminuria.	No
39	ZOPPINI et al. 2009	Italy	Verona Diabetes Study	1987	5	**T2D**	Evaluate the effects of plasma **HDL-C levels** on the incidence of CKD	GFR	ESRD, †	Pts who developped incident CKD were older, more likely to be female, obese, longer diabetes duration, albuminuria, retinopathy. **They had lower eGFR and HDL level at baseline.** No significant difference in LDL-C in non CKD and CKD groups.	No
15	ROSSI et al. 2010	Italy	DEMDAND study	1019	1	**T2D,** 18-80y	Investigate the role of obesity in predicting changes in AER	Progression MiA to MaA	-	27% had ACR progression and 23.7% regression. Waist circumference and BMI were associated with progression of albuminuria.	No
43	RURALI et al. 2013	Italy	BENEDICT	1163	3.6	**T2D**	Evaluate the interactive role of Pro618Ala ADAMTS13 polymorphism (lower serum levels of ADAMTS13) and ACEi therapy in the prediction of new onset MiA	Mia ; MaA	CV events, †	17.3% Ala carriers and 82.7% were Pro/Pro homozygotes. Ala carriers were the pts with the highest risk of renal events on non-ACEI but were the one who benefited more from ACEi therapy.	**Yes (genetics)**
36	STADLER et al. 2006	Austria	-	648	20	newly diagnosed **T1D** dg <30y	Investigate the predictive risk factors of † and RRT in T1D pts after 20y of observation	albumunuria	RRT; †	13% of the pts died ; 5.6% received RRT. Higher risk for the endpoints when presence of DN and poor glycemic control increased risk for endpoint. is poor. Target of < 8.5% HbA1c for prevention of RRT.	No
41	SAULNIER et al. 2014	France	SURDIAGENE	522	2	**T2D** ; with DN	Identify the genetic and environmental determinents of complications in T2D. Evaluate the prognostic value of serum TNFR1 concentration	doubling of baseline serum creatinine	ESRD	196 † occured during the follow-up. High serum TNFR1 was associated with a higher risk of all cause of † .	**Yes (genectics)**
44	JAZIRI et al. 2010	France	SURDIAGENE				Analyse the association of three adiponectin gene (ADIPOQ) polymorphisms and isoforms of circulating adioponectin with the risk of nephropathy			No significant association between renal events and any of SNPs. Nevertheless, the -11391A/+45G/+276G haplotype was significantly associated with a higher risk of renal events.	
35	SALINERO-FORT et al. 2015	Spain	MADIABETES Study	3443	5	**T2D**; >30y	Evaluate the incidence rate and risk factors of CKD stage 3-6 in T2D	eGFR <60 at any visit or average successive eGFR < 60 among subjects free of CKD at baseline	†	Cumultative 5y incidence of CKD was 10.2%. The greatest risk is observed in pts over 75y, with T2D duration ≧10y, with HT, albuminuria ≧ 300mg/g , SBP ≧ 150mmHg, dyslipidemia and AMI.	**Yes (genetics)**

To summarize both tables, we can highlight the following essential observations. The majority of cohort studies were undertaken with T2DM patients (n=17) and only a few with T1DM patients (n=4). There were 4 registries, among which two were undertaken with T2DM patients and two with T1DM patients.

The most active European countries with cohorts in DN were: Finland (11)(12)(13)(14)(15)(16), Italy (17)(18)(19)(20)(21), Germany (22)(23), Sweden/Denmark (24)(25)(26)(27)(28), Netherlands (29)(30) and Spain. The most active European countries with registries were Finland (31), Sweden (32), UK (33) and Italy (34). Only 7 cohort studies mentioned the presence of a biobank and only two studies published genetic results (BENEDICT and SURDIAGENE) during the last 10 years.

FinnDiane is a type 1 diabetes cohort with a genetic biobank. We considered it as a cohort, keeping in mind the following definition: “a registry can be used to construct a cohort”. Finland collects all the database from all over the country about the T1DM patients and then follow up the population (11)(12)(13)(14)(15)(16).

Briefly, these recent publications led to the following observations.

Mortality increases with reduced eGFR in diabetic patients. Patients with long duration of T2DM or advanced age showed higher cumulative incidence of chronic kidney disease than patients who were recently diagnosed (35). Higher HbA1c values, presence of microalbuminuria or macroalbuminuria or/and lower creatinine clearance at baseline were shown to be markers of higher mortality (36). RIACE study suggests that HbA1c variability affects CKD more than average HbA1c (37). UKPDS 74 identify systolic blood pressure and Indian-Asian ethnicity as risk factors for renal impairment (38).

New biomarkers of renal impairment were identified and are listened below.

Concerning the serum/plasma markers, higher plasma level of HDL-C was associated with reduced incidence of CKD in a large cohort of T2DM patients called the Verona Study. They concluded in a multiple regression analysis that higher HDL-C levels were associated with a lower risk of CKD, with 24% reduction in the risk of every SD (10mg/dl) increase HDL-C independently of several potential confounders (39).

The GO-DARTS study identified 14 plasma biomarkers that contained most of the predictive information beyond clinical covariates, such as beta2-microglobulin, cystatin C, FGF-21, uracil. The strongest predictor was symmetric dimethylarginine and asymmetric dimethylarginine ratio (SDMA/ADMA) (40). High level of TNFR1 in the serum has been identified as a biomarker (41). Higher concentrations of individual biomarkers like MMP2, MMP7,YKL-40, NFR1, NPHS2 and endostatin were significantly associated with eGFR decline (42).

New urinary markers like u-KIM1/Cr and uGpnmb/Cr ratios correlated with the severity of proteinuria and were associated with a faster decline in renal function in T1DM patients. However,

neither provided additional information predicting development from microalbuminuira to macroalbuminuria during the follow-up.

Finally, genetics markers were studied. BENEDICT, an Italian cohort, reported genetic analysis (43). They evaluated the interactive role of Pro618Ala ADAMTS13[2] polymorphism (lower serum levels of ADAMTS13) and ACEi therapy in the prediction of renal events. They concluded that Ala carriers were the patients with the highest risk of renal impairment on non ACEi but were also those who benefited most from the ACEi therapy (43). A group of investigators analysed SURDIAGENE, a French cohort, to replicate their findings with an other trial named DIABHYCAR, also a French cohort with T2DM subjects and high urinary albumin concentration (44). They evaluated the consequences of variants of adiponectin gene and their plasma concentrations on the risk of renal failure in T2DM patients. In SURDIAGENE, they showed an association between the haplotype containing the two high-risk alleles with renal events. High adiponectin concentrations associated with these two gene variants may be the cause, rather than a consequence of renal failure in these subjects.

4.7.2 Vascular research

Among **the 11 studies identified with vascular markers** in DN, 3 were prospective and 8 cross-sectional.

Table 5. Vascular prospective cohorts

Ref	First author	Country	Name of the cohort	Number of subjects	Median follow up	Inclusion criteria	Exclusion criteria	Objective	Measured markers	Renal Endpoints	Results
45	BRUNO et al. 2015	Italy	-	70 (43 T2D/27 hypertensive)	4.1y	**T2D** or essential hypertension and normal AER within the previous 6 months, 40-70y, absence of any micro or macrovascular complications	Previous or current ttt with antihypertensive or antidiabetic medications	Investiguate if **DRIN (dynamnic renal resistive index),** or other markers of systemic vascular damage are able to predict albuminuria onset and eGFR decline in newly diagnosed T2D or hypertension pts	**RI** (resistance index), **FMD** (flow-mediated dilation of brachial artery), carotid-femoral **PWV**, **AIx**, **DRIN** (change in RI after sublingual nitrate administration).	eGFR ; ACR	RI and DRIN values were significantly higher in T2D as compared to EH. **DRIN and PWV were significantly higher in pts developing MiA while RI did not differ significantly**. In the diabetic sub-group DRIN was a better predictor of developing microalbumuria than PWV, while the opposite occurred in the hypertensive subgroup.
47	SEDAGHAT et al. 2015	Netherlands	ROTTERDAM study	3666 (7.6% T2D)	11y	Living Ommoord district in the city of Rotterdam (55y-106y) with available data on arterial stiffness markers and creatinine measurements at baseline		Investigate the association of indicators of arterial stiffness with kidney function decline	PWV; carotid stiffness; heart rate ; genetic data	Free of CKD at baseline (eGFR >60ml/min/1.73m2) with a decline in eGFR <60 between the 2 examinations.	Observed an association between pulse pressure and decline in kidney function but no association between PWV and CKD after adjustement for cardiovascular risk factors. PP genetics variants but not PWV genetic variants are associated with kidney function decline.
46	GOMEZ-MARCOS et al. 2011	Spain	LOD-DIABETES	**112 (n= 68 T2D, n=44 Mets)**	4y	**T2D** or MetS	Unable to comply with the protocol	Evaluate the prognostic value of **central arterial pressure and PWV** with target organ damage (renal, cardiac, vascular)		eGFR	yet not published

[2] ADAMTS13 : a disintegrin and mealloprotease with thrombospondin type 1 repeats, member 13. Impaired ADAMTS13 proteolysis of von Willebrand factor multimers may accelarate renal and cardiovascular complications.

Table 6. Cross-sectional vascular studies

Ref	First author	Country	Number of subjects	Inclusion criteria	Exclusion criteria	Objective	Measured markers	Renal Endpoints	Results
48	MANCINI et al. 2013	Italy	88	**T2D** > 1y ; mild coexistent HT ; BMI ≤ 40 kg/m^2 - Non diabetic controls	BMI >40kg/m^2 ; pts with severe renal artery stenosis	Evaluate the renal volume and intrarenal hemodynamics in diabetic pts with normal renal function in comparison to nondiabetic controls	Renal volume ; **RI (resistance index)** of segmental arteries	eGFR ; ACR	Diabetic pts had mean renal volume, renal area index and RI values significantly higher than controls. Higher RI values (>0.75) were associated with longer diabetes duration and had greater protein urinary excretion and was correlated with the albuminuric stage.
49	PETRICA et al. 2015	Romania	70	**T2D** ; DM > 5y ; ttt with OAD; NA [UACR <30mg/g] or MiA [UACR >30mg/g]	Symptoms and/or history of cerebrovascular disease. Stenoses or occlusions in the vessels examined	Evaluate the pattern of endothelial dysfunction in the kidney and the brain	Evaluated the endothelial variabiltiy in relation to **AGE** (advanced glycation end product)-**modified peptides ADMA** (plasma Concentration of Asymmetric Dimethylarginine) as a biomarker of endothelial dysfunction. **Cerebral hemodynamics** were measured by ultrasounds.	UACR ; eGFR	Plasma-ADMA showed no correlation with UACR, but only with high-hsCRP, plasma AGE, serum cystatin C, eGFR, and DM duration. Data showed a signifiant correlations of cerebral hemodynamics indices with cystatin C, hsCRP, DM duration.
50	STRÒZECKI et al. 2013	Poland	60 pts with CKD (24 DN/36 nondiabetic CKD)	**T2D** ; T1D	Immunosuppresive ttt; overt infection	Investigate the relationship between plasma **AGE (Advanced glycation end products)** concentration and arterial stiffness in nondialyzed pts with DN and those with non-diabetic CKD	**AGE, PWV**	eGFR ; ACR	The AGE concentration was significantly higher in pts with DN compared with those with CKD without diabetes and controls. PWV was also significantly higher in pts with DN compared with those without diabetes ; In a multiple regression analysis, PWV was independently associated with age, DN, and SBP, but not with AGEs.
51	NAKA et al. 2012	Greece	165	**T2D,** 40-80y ; ttt with OAD medications or/and insulin for at least 6 months prior to study enrollment.	History of macrovascular disease, microvascular disease, chronic heart failure, liver disease . Anemia ; thyroid dysfunction or other endocrine diseases ; alcoholism	Investigate the predictors of vascular dysfunction in T2D pts.	Brachial artery flow-mediated dilation **(FMD);** Nitrate mediated dilation **(NMD), PWV**	eGFR ; ACR	Increased duration of diabetes was found to be the single independent predictor of **decreased FMD (Brachial artery flow-mediated dilation)** ; increased age and FPG (fasting plasma glucose) and the presence of HT were independent predictors of **decreased NMD** (endothelium-independent, nitrate-mediated vasodilatation). Increased age and SBP were independently associated with **increased PWV.**
55	HERMANS et al. 2007	Netherlands Hoorn Study	806	**T2D**		Investigate the association of impaired renal function with arterial stiffness	Peripheral arterial stiffness and central arterial stiffness	eGFR ; ACR	Lower eGFR was associated with a **lower distensibility coefficient of the carotid and brachial artery**.Greater UACR (per quartile) was associated with a greater Einc (indicator of the intrinsic wall properties) and a trend to a lower distensibility coefficient of the carotid artery.
53	THEILADE et al 2014	Denmark	676	**T1D**	ESRD	Investigate associations between the pulse-wave-derived measures augmentation pressure (AP) and Aix (Augmentation Index), and diabetic complications in T1D	**AP ; Aix ; PWV ; PP** (pulse pressure)	UAER ; eGFR	AP & AIx were significantly lower in patient with short duration of diabetes (<10y) and NA pts
52	THEILADE et al. 2013	Denmark	676 (including 15 controls)	**T1D**	T2D	Investigated the association between arterial stiffness and diabetes complications	Aortic **PWV**	eGFR ; MiA, MaA	PWV correlated with age, diabetes duration, UAE, heart rate, and BP.
54	GORDIN et al. 2012	Finland FinnDiane	622 T1D & 185 nondiabetic	**T1D**	-	Examine associations between arterial stiffness and diabetic complications in pts with T1D	**Aix**	UAER	Assococation between Aix and DN were significant. Pts with T1D without signs of DN (UAER normal) had stiffer arteries measured as the Aix than age-matched control subjects

4.7.2.1 Vascular cohorts

The major goal in the prospective studies was to assess whether peripheral vascular functional markers predicted eGFR decline.

Among the **three prospective studies** that were found (Table 5), some results suggested that the predictive value of dynamic renal resistive index (DRIN) appears to be superior to systemic vascular biomarkers such as PWV for prediction of microalbuminuria onset, when measured in newly diagnosed, untreated patients with T2DM (45).

The LOD-DIABETES study evaluates the progression of cardiovascular disease assessing subclinical vascular risk factors (carotid intima-media thickness, pulse wave velocity and ankle/brachial index) in two different populations (T2DM and Metabolic syndrome subjects). It assesses the vascular markers but has not yet published any results concerning the decline of the kidney function (46).

The Rotterdam Study, a cohort with only 7.6% of diabetic patients, observed an association between pulse pressure and decline in kidney function (47). There was no association between pulse wave velocity (femoral and carotid artery) and annual decline in eGFR.

4.7.2.2 Vascular cross-sectional studies

8 cross-sectional studies were undertaken with T2DM patients (n=5) and T1DM patients (n=3) with the objective of analysing vascular markers and renal markers and their association with the decline in kidney function (Table 6).

These studies were conducted in Italy (48), Romania (49), Poland (50), Greece (51), Denmark (52)(53) and Finland (54). A study conducted in the Netherlands, called the Hoorn study, suggests that a lower eGFR is associated with a lower distensibility coefficient of the carotid and brachial artery, therefore subjects with renal impairment are independently associated with greater arterial stiffness (55).

Another study, conducted in Italy suggested that the risk of developing DN begins before the modification of urinary albumin excretion. It can be identified with increased renal volume and higher resistance index using a duplex sonography (48).

As they are cross-sectional studies, neither of them had a genetic database.

4.8 Conclusion

To conclude, most prospective cohort studies of DN in Europe involve T2DM patients and do not examine vascular or genetic parameters. However, they are important as they are designed to identify novel markers contributing to the decline in renal function. However, the results reported in these studies need confirmation in different populations before they can be validated as screening methods for diabetic nephropathy in clinical practice.

Part 2

5 Lausanne prospective cohort on diabetic nephropathy: SWIDINEP

In the second part of this Master thesis, we wanted to compare the data we had previously collected with a local prospective cohort study conducted in Lausanne, Switzerland.

5.1 Aim

The aim of this cohort, named SWIDINEP (Swiss diabetic nephropathy cohort), is to follow type 1 and type 2 diabetic patients with CKD stage 1-5[2] at baseline, 2y and 5y with clinical, biochemical, genetic and vascular characterization and to identify markers involved in renal function decline.

5.2 Patients: inclusion and exclusion criteria

Patients are recruited in the Nephrology and Diabetology ambulatory clinics at the CHUV in Lausanne.

The patients are selected if they are diabetic, over 18 years old, with a eGFR < 60 mL/min/1.73 m^2 or (micro)albuminuria ≥ 30 mg/24h (alternatively on a urinary spot albumin/creatinine ratio ≥ 2.5 mg/mmol for men and ≥ 3.5 mg/mmol for women). The patients are asked to sign a consent form stating their understanding of the protocol.

Patients under 18 years old, presenting a non-diabetic renal disease, or unable to give their consent are excluded from the cohort.

5.3 Data collection

A doctor in an ambulatory diabetic and nephrology consult sees all the patients who enter this study. At baseline, blood sample, DNA and urine are taken and stored in the bio bank.

During the follow-up, clinical and historical parameters will be collected, such as blood pressure, weight and micro- and macrovascular complications. Blood glucose control will be assessed by the HbA1C level. Treatment taken by the patient will also be updated.

Some data was missing for the analysis and we needed to look for it in the patients' files in order to be complete. If nothing was found, we would contact their general practitioners.

5.4 Statistical analysis

Descriptive statistics were made with the help of Excel.

Table 7. Comparison of diabetic nephropathy cohort

Cohort	Author	Number of subjects	Mean age (y)	Sex (men%)	Ethnicity caucasian	BMI [kg/m2]	eGFR [mL/min/1.73 m2]	ACR [mg/mmol]	UAE (> 30 mg/24h)	Diabetic type	DM duration (y)	HbA1c level [DCCT%]	Hypertension (%)	*Mean ambulatory diurnal [mmHg]*	*Noctural systolic/diastolic BP [mmHg]*	On RAS blockade - antihypertensive ttt (%)	Total Cholesterol TG [mmol/L] [mmol/L]		HDL	LDL cholesterol [mmol/l]	Active smoking (%)	On aspirin (%)	Biobank
SWIDINEP		**128**	**63**	**73%**	**82%**	**32**	**61**	**51.4**	**52% MiA 27% MaA**	**T2D (++)**	**15**	**7.8**	**98**	**126/75**	**120/70**	**92**	**4.4**	**2.4**	**1.2**	**2.10**	**20.6**	**72**	**Yes**
Summary of prospective european cohort studies (min-max)		**82-6534**	**47-74**	**53-78%**	**82-100%**	**25 - 33**	**47 - 90**	**1.17-28.5**	**9.8%-59% MiA**		**8.0 - 18**	**7.1 - 7.8**	**33 - 100**	**124-144/69-83**		**43-98**	**5.3 - 5.4**	**1.6 - 2.0**	**1.2 - 1.4**	**2.0 - 5.4**	**7.3 - 35.8**	**49 - 93**	
UKPD 74	RETNAKARAN et al. 2006	5102	52	59%	82%	28	*NA*	*NA*	*NA*	T2D	*NA*	7.2	*NA*	135/83	*NA*	*NA*	*NA*	*NA*	*NA*	5.40	31.0	*NA*	**Yes**
ET2DS UK	CONWAY et al. 2012	978	68	53%	*NA*	*NA*	72	1.17	15% MiA	T2D	*NA*	7.4	*NA*	133/69	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	No
GODARTS Scotland	LOOKER et al. 2015	154 cases	74	43%	*NA*	31	48	*NA*	45.1 % (albuminuria)	T2D	9	7.3	*NA*	144/71	*NA*	96	*NA*	*NA*	*NA*	*NA*	11.1	*NA*	**Yes**
ESTHER Germany	SCHÖTTKER et al. 2013	3538 (490 diabetes)	63	57%	*NA*	29	89	*NA*	*NA*	T2D	*NA*	*NA*	*NA*	140/-	*NA*	64	5.4	*NA*	*NA*	*NA*	14.3	*NA*	No
PREVEND MetS negatif Germany	VAN DER VELDE et al. 2011	6534 (76%)	47	46%	95%	25	82	*NA*	10.7% MiA	T2D	*NA*	*NA*	33	124/72	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	38.8	*NA*	No
PREVEND MetS positif Germany		2058 (24)	56	62%	97%	30	78	*NA*	28.6% MiA	T2D	*NA*	*NA*	78	143/79	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	35.1	*NA*	No
DIACORE Germany	DÖRHÖFER et al. 2013	aim 6000	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	**Yes**
Denmark	NIELSEN et al. 2012	177	59	75%	*NA*	33	90	*NA*	59 % MiA	T2D	12±7	7.8	*NA*	130/75	*NA*	98	*NA*	*NA*	*NA*	*NA*	*NA*	93	No
PREDICTIONS Denmark	PENA et al. 2015	82	64	54%	100%	32	78	1.2	NA	T2D	15 ±7	7.7	*NA*	135/72	*NA*	43	*NA*	*NA*	1.3	2.00	9.6	*NA*	No
RIACE Italy	PUGLIESE et al. 2011	4062	66	60%	*NA*	28	82	*NA*	22.3 % MiA	TD2	10	7.29	84	140/80	*NA*	60	*NA*	*NA*	*NA*	2.60	16.6	*NA*	No
Observational study Italy	FABBIAN et al. 2015	1284	67	57%	100%	*NA*	72	*NA*	9.8 % MiA	T2D	*NA*	*NA*	72	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	No
Verona Diabetes Study Italy	ZOPPINI et al. 2012	1682 (263 rapid decliners)	67	63%	100%	29	78	*NA*	*NA*	T2D	16 ±9	7.6	94	142/81	*NA*	*NA*	*NA*	1.62	*NA*	3.33	28.9	*NA*	No
Verona Diabetes Study Italy	ZOPPINI et al. 2008	1987 (234 CKD at follow-up)	72	53%	100%	29	84	*NA*	*NA*	T2D	17±9	7.8	*NA*	142/80	*NA*	*NA*	*NA*	1.6	1.4	3.40	21.3	56	No
DEMAND Italy	ROSSI et al. 2009	1289	65	64%	100%	31	82	*NA*	*NA*	T2D	11 ±9	7.8	*NA*	141/81	*NA*	*NA*	5.3	2	1.2	3.20	17.6	NA	No
BENEDICT	RURALI et al. 2013	1163	62	55%	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	**Yes**
SURDIAGENE France	SAULNIER et al. 2014	522	70	57%	*NA*	31	49	28.5	*NA*	TD2	18±10	7.7	*NA*	137/ 72	*NA*	73	*NA*	*NA*	*NA*	4.93	7.3	*NA*	**Yes**
MADIABETES Spain	SALINERNO-FORT et al. 2015	2620	67	55%	*NA*	30	*NA*	*NA*	*NA*	T2D	8±7	7.1	70	133/77	*NA*	*NA*	*NA*	*NA*	*NA*	4.90	18.1	49	No

Table 8. Comparison of vascular research

Vascular Cohort	Author	Number of subjects	Mean age (y)	Sex % (men)	Ethnicity caucasian	BMI [kg/m2]	eGFR [mL/min /1.73 m2]	Diabetic type	DM duration (y)	HbA1c %	Smoking %	SBP/DBP (mmHg)	Creatinine (mmol/l)	TC (mmol/l)	TG (mmol/l)	HDL (mmol/l)	LDL (mmol/l)	Kidney resistance indexes	fa-PWV (m/s)	ba-PWV (m/s)	Left carotid IMT (mm)
SWIDINEP		**128**	**63**	**73.40**	**82%**	**31**	**62**	**T2D (++)**	**15**	**7.8**	**21**	**126/75**	**75.7**	**4.4**	**2.4**	**1.2**	**2,1**	**0.77**	**11.8**		**0.78**
Summary of prospective cohorts with vascular caracterization		**27-279**	**60-65**	**51-63.2**		**27-30**	**79-88**			**6.8-6.9**	**19-24**		**75.7**	**4.8-6.4**	**1.6-1.9**	**1.3**	**2.8-3.4**		**7.8-9.6**	**9.6-12.2**	
LOD-DIABETES STUDY	GOMEZ-MARCOS et al. 2010	112 (T2DM 68; MetS 44)	60	63.2	*NA*	30	88	T2D	5.4	6.8	24	136/82	75.7	4.8	1.6	1.3	2.8	*NA*	9.6	9.6	0.76
Italy	BRUNO et al. 2015	27	60	52	*NA*	30	86	T2D	*NA*	6.9	19	139/78	75.7	5.8	1.9	1.3	3.4	0.57 (pts with MiA)	7.8 (pts with MiA)	*NA*	*NA*
Rotterdam Study	SEDAGHAT et al. 2015	3666 (279 DM)	65	51	100%	27	79	diabetes 7.6%	*NA*	*NA*	21	137/75	*NA*	6.4	*NA*	1.3	*NA*	*NA*	*NA*	12.2	*NA*

7 Comparison with the literature research

We created two tables that compare **the European prospective cohort and vascular studies** with SWIDINEP (Table 7 & 8).

As the majority of patients included in SWIDINEP are T2DM (96.5%), we chose to simplify the comparison to cohorts with T2DM patients (n=15).

7.1 Epidemiological comparison

We listed all the clinical characteristics of subjects included in the prospective cohort studies as well as in the prospective vascular cohort studies and we established an interval with a minimum and a maximum that we used for the comparison.

The number of subjects included in the SWIDINEP cohort was in the lower range of those included in the prospective cohort studies. In contrast to that, the number of subjects corresponded better to those included in the prospective vascular cohort studies.

The mean age of the SWIDINEP subjects is in the middle range compared to the other prospective cohorts. The same conclusion can be found for the vascular cohorts.

The impact of age at onset of diabetes on the risk of developing nephropathy and end-stage renal disease is still unclear. For example, a study conducted in Australia shows an important association between increased age along increased duration of the diabetes and the risk of developing albuminuria among type 2 diabetes patients (56).

Most of the cohorts are composed of a predominance of male subjects. This can also be observed in the vascular characteristic cohorts. SWIDINEP is situated in the upper range of those included in our general and vascular cohorts, and therefore we have to keep in mind that all the conclusions that have been made up to now are more accurate for the male sex.

Nearly all of the subjects in the cohorts are Caucasians. This can be explained by the fact that all the cohorts have been conducted in Europe. In SWIDINEP, 82% of the subjects are of Caucasian background, which is in the lower range of the interval.

It is important to consider the factor of the race, as it has been shown that the incidence and the severity of diabetic nephropathy are higher in Africans (3- to 6-fold compared to Caucasians), Mexican-Americans and Pima Indians with type 2 diabetes (57)(58)(59). These differences suggest a primary role of socioeconomics factors such as diet, poor control of hypoglycaemia, hypertension and obesity, which are more found in those populations (60).

SWIDINEP subjects have a BMI of 31.4 kg/m^2, which is situated in the higher range of this measure among the vascular and general cohorts. This characteristic should be taken into consideration as it has a great value for the cardiac and renal comorbidities. There have been studies showing that a

high body mass index can be associated with an increased risk of chronic kidney disease among patients with diabetes (56)(61)(62).

As for the glycaemic control, the mean HbA1c level in SWIDINEP is in the higher range compared to the other studies. It is more emphasized when compared to the cohorts with vascular assessment, where the mean HbA1c level is beyond the given interval.

In the SWIDINEP study, 98 % of the subjects have hypertension, which is situated in the higher range of all the percentages. However, some studies did not specify the percentage of the subjects suffering from hypertension.

In relation to the prevalence of smoking, 20.6% of the SWIDINEP subjects are active smokers, which is in the higher range compared to the other studies. Smoking has many adverse effects on diabetic patients. This includes evidence of increasing albuminuria and the risk of end-stage renal disease. When it comes to dialysis, it decreases survival (63).

The decline of the kidney function can be evaluated by the mean eGFR value. SWIDINEP subjects are situated in the range of eGFR value compared to other cohort studies. When compared to vascular cohorts, the mean value is the lowest and consequently out of the range. This indicates that the subjects from SWIDINEP are in a more advanced stage of renal damage.

In general, all of the cohorts only mentioned whether the subjects had normal albuminuria, microalbuminuria or macroalbuminuria. They did not indicate the albumin creatinine ratio nor urinary albumin excretion value in their baseline characteristics, which could therefore not be interpreted. Only three of them mentioned it and the SWIDINEP data were superior to those values.

The Italian cohort RIACE shows that non-albuminuric renal impairment is a predominant form of stage >3 CKD in their study (n=10.6 %) (64). This finding supports new observations made in recent studies, which show that there is a shift of the phenotype of renal impairment among type 2 diabetes with a growing of prevalence of non-albuminuric CKD form. Another group, Pavkok et al, noticed that the proportion of patients' CKD without albuminuria increased over 20 years (65). They suggest an increase of the proportion of patients on hypoglycemic and/or antihypertensive therapy agents, especially ACE inhibitors or ARBs, which can be associated with the rise of non-albuminuric CKD patients.

Concerning the lipid status, in both vascular and renal cohorts, SWIDINEP's subjects have the lowest lipid values (HDL and total cholesterol) and are out of the range.

7.2 Vascular parameters

Vascular comparison was problematic as it was difficult to find studies with the same objective, therefore only a small quantity of information could be found. One of the comparable values was the pulse wave velocity. The value of fa-PWV is higher in SWIDINEP group and compared to the three others is not in the range.

An interesting study was found called The Rotterdam Study, a cohort with non-diabetic subjects (47). Only 7.6% of the Rotterdam Study suffers from diabetes. Nevertheless, we kept it as the studied vascular markers were relevant. Rotterdam Study is the only one that has a genetic database.

8 Conclusion

To conclude, the literature review helped us bring to light the variety of studies that have been conducted up to this date in Europe. The majority of the prospective studies were done in Finland, Italy, Sweden, but also in France, the UK and Spain. Several conclusions of the article had already been known and well-established. Nevertheless, there were also new markers that were identified and studied. However, to obtain a more precise conclusion and to use them as biomarkers, we still need to study them in large cohorts with a long-term follow-up.

We have to remain attentive to the methods that the studies used. Not every study was well described for the exclusion criteria or, for instance, the endpoints. Those criteria should not be neglected, as they are important to judge the rigorous analysis of a study.

Concerning the second part of this thesis, the main goal was to find out if there were any other cohorts that were conducted in Europe with the same objective and method as the SWIDINEP study. Information and genetic data can be exchanged with comparable cohorts. SWINIDEP is a small-sized cohort for now but its studied markers are very precise and could help predicting renal progression.

We were able to find studies like ET2DS UK (66), LOD DIABETES, SURDIAGENE and MADIABETES that correspond to our SWINDINEP data base.

This is a vast subject and it has various implications. Diabetes does not only have negative effects on renal function but also on other organs, with retinopathy and cardiac issues as examples. This implies the need for overall medical care of the diabetic patient and shows that early intervention on the patient has clear benefits for their survival.

9 Acknowledgments

We would like to thank the patients who participated in the SWIDINEP cohort follow-up. We would also like to thank Madame Nobre, clinical nurse in CHUV, for her help in collecting all the data of the SWIDINEP follow-up as well as Madame Elmers, reference librarian in CHUV, who contributed to the literature review.

10 References

1. Hulley SB, Cummings SR, Browner WS, Grady DG, Newman TB. Designing Clinical Research. Lippincott Williams & Wilkins; 2013. 611 p.

2. Mann CJ. Observational research methods. Research design II: cohort, cross sectional, and case-control studies. Emerg Med J EMJ. 2003 Jan;20(1):54–60.

3. Gliklich RE, Dreyer NA, Leavy MB, editors. Registries for Evaluating Patient Outcomes: A User's Guide [Internet]. 3rd ed. Rockville (MD): Agency for Healthcare Research and Quality (US); 2014 [cited 2016 Oct 30]. (AHRQ Methods for Effective Health Care). Available from: http://www.ncbi.nlm.nih.gov/books/NBK208616/

4. Registry Studies: Why and How [Internet]. CDG Whitepapers. [cited 2016 Oct 30]. Available from: http://clinicaldevice.typepad.com/cdg_whitepapers/2011/07/registry-studies-why-and-how.html

5. Gariani K, de Seigneux S, Pechère-Bertschi A, Philippe J, Martin PY. Néphropathie diabétique. Rev Médicale Suisse. 2012;8(330):473–9.

6. Tuttle KR, Bakris GL, Bilous RW, Chiang JL, de Boer IH, Goldstein-Fuchs J, et al. Diabetic kidney disease: a report from an ADA Consensus Conference. Am J Kidney Dis Off J Natl Kidney Found. 2014 Oct;64(4):510–33.

7. Waanders F, Visser FW, Gans ROB. Current concepts in the management of diabetic nephropathy. Neth J Med. 2013 Nov;71(9):448–58.

8. Information NC for B, Pike USNL of M 8600 R, MD B, Usa 20894. Diabetic nephropathy: diagnosis, prevention, and treatment. - PubMed - NCBI [Internet]. [cited 2015 Sep 9]. Available from: https://crypto.unil.ch/pubmed/,DanaInfo=www.ncbi.nlm.nih.gov+15616252

9. Ahmad J. Management of diabetic nephropathy: Recent progress and future perspective. Diabetes Metab Syndr. 2015 Mar 6;

10. Association AD. Standards of Medical Care in Diabetes—2014. Diabetes Care. 2014 Jan 1;37(Supplement 1):S14–80.

11. Panduru NM, Saraheimo M, Forsblom C, Thorn LM, Gordin D, Wadén J, et al. Urinary Adiponectin Is an Independent Predictor of Progression to End-Stage Renal Disease in Patients With Type 1 Diabetes and Diabetic Nephropathy. Diabetes Care. 2015 May 1;38(5):883–90.

12. Thorn LM, Gordin D, Harjutsalo V, Hägg S, Masar R, Saraheimo M, et al. The Presence and Consequence of Nonalbuminuric Chronic Kidney Disease in Patients With Type 1 Diabetes. Diabetes Care. 2015 Nov;38(11):2128–33.

13. Wadén J, Tikkanen HK, Forsblom C, Harjutsalo V, Thorn LM, Saraheimo M, et al. Leisure-time physical activity and development and progression of diabetic nephropathy in type 1 diabetes: the FinnDiane Study. Diabetologia. 2015 May;58(5):929–36.

14. van der Kloet FM, Tempels FWA, Ismail N, van der Heijden R, Kasper PT, Rojas-Cherto M, et al. Discovery of early-stage biomarkers for diabetic kidney disease using ms-based metabolomics (FinnDiane study). Metabolomics Off J Metabolomic Soc. 2012 Feb;8(1):109–19.

15. Forsblom C, Harjutsalo V, Thorn LM, Waden J, Tolonen N, Saraheimo M, et al. Competing-Risk Analysis of ESRD and Death among Patients with Type 1 Diabetes and Macroalbuminuria. J Am Soc Nephrol. 2011 Mar 1;22(3):537–44.

16. Groop P-H, Thomas MC, Moran JL, Waden J, Thorn LM, Makinen V-P, et al. The Presence and Severity of Chronic Kidney Disease Predicts All-Cause Mortality in Type 1 Diabetes. Diabetes. 2009 Jul 1;58(7):1651–8.

17. Penno G, Solini A, Zoppini G, Orsi E, Zerbini G, Trevisan R, et al. Rate and Determinants of Association Between Advanced Retinopathy and Chronic Kidney Disease in Patients With Type 2 Diabetes. Diabetes Care. 2012 Nov 1;35(11):2317–23.

18. Pugliese G, Solini A, Fondelli C, Trevisan R, Vedovato M, Nicolucci A, et al. Reproducibility of albuminuria in type 2 diabetic subjects. Findings from the Renal Insufficiency And Cardiovascular Events (RIACE) study. Nephrol Dial Transplant. 2011 Dec 1;26(12):3950–4.

19. Fabbian F, De Giorgi A, Monesi M, Pala M, Tiseo R, Forcellini S, et al. A possible relationship between renal impairment and complications development in type 2 diabetes mellitus: a prospective, observational study in Italy. J Diabetes Complications. 2015 Aug;29(6):771–5.

20. Zoppini G, Targher G, Chonchol M, Ortalda V, Negri C, Stoico V, et al. Predictors of estimated GFR decline in patients with type 2 diabetes and preserved kidney function. Clin J Am Soc Nephrol CJASN. 2012 Mar;7(3):401–8.

21. Rossi MCE, Nicolucci A, Pellegrini F, Comaschi M, Ceriello A, Cucinotta D, et al. Obesity and changes in urine albumin/creatinine ratio in patients with type 2 diabetes: The DEMAND Study. Nutr Metab Cardiovasc Dis. 2010 Feb;20(2):110–6.

22. Schöttker B, Brenner H, Koenig W, Müller H, Rothenbacher D. Prognostic association of HbA1c and fasting plasma glucose with reduced kidney function in subjects with and without diabetes mellitus. Results from a population-based cohort study from Germany. Prev Med. 2013 Nov;57(5):596–600.

23. Dörhöfer L, Lammert A, Krane V, Gorski M, Banas B, Wanner C, et al. Study design of DIACORE (DIAbetes COhoRtE) - a cohort study of patients with diabetes mellitus type 2. BMC Med Genet. 2013;14:25.

24. Nielsen SE, Hansen HP, Jensen BR, Parving H-H, Rossing P. Urinary Neutrophil Gelatinase-Associated Lipocalin and Progression of Diabetic Nephropathy in Type 1 Diabetic Patients in a Four-Year Follow-Up Study. Nephron Clin Pract. 2011;118(2):c130–5.

25. Andrésdóttir G, Bakker SJL, Hansen HP, Parving H-H, Rossing P. Urinary sulphate excretion and progression of diabetic nephropathy in Type 1 diabetes. Diabet Med J Br Diabet Assoc. 2013

May;30(5):563–6.

26. Nordwall M, Abrahamsson M, Dhir M, Fredrikson M, Ludvigsson J, Arnqvist HJ. Impact of HbA $_{1c}$, Followed From Onset of Type 1 Diabetes, on the Development of Severe Retinopathy and Nephropathy: The VISS Study (Vascular Diabetic Complications in Southeast Sweden). Diabetes Care. 2015 Feb;38(2):308–15.

27. Svensson MK, Tyrberg M, Nyström L, Arnqvist HJ, Bolinder J, Östman J, et al. The risk for diabetic nephropathy is low in young adults in a 17-year follow-up from the Diabetes Incidence Study in Sweden (DISS). Older age and higher BMI at diabetes onset can be important risk factors: Diabetic Nephropathy in Young Adults. Diabetes Metab Res Rev. 2015 Feb;31(2):138–46.

28. Torffvit O. The effect of achieving a systolic blood pressure of 140 mmHg. A prospective study of ambulatory measurements in type 2 diabetic patients with nephropathy. J Diabetes Complications. 2012 Dec;26(6):540–5.

29. van der Velde M, Bello AK, Brantsma AH, Nahas M El, Bakker SJL, de Jong PE, et al. Do albuminuria and hs-CRP add to the International Diabetes Federation definition of the metabolic syndrome in predicting outcome? Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc. 2012 Jun;27(6):2275–83.

30. Pena MJ, Lambers Heerspink HJ, Hellemons ME, Friedrich T, Dallmann G, Lajer M, et al. Urine and plasma metabolites predict the development of diabetic nephropathy in individuals with Type 2 diabetes mellitus. Diabet Med J Br Diabet Assoc. 2014 Sep;31(9):1138–47.

31. Finne P, Reunanen A, Stenman S, Groop P-H, Grönhagen-Riska C. Incidence of end-stage renal disease in patients with type 1 diabetes. JAMA. 2005 Oct 12;294(14):1782–7.

32. Svensson MK, Cederholm J, Eliasson B, Zethelius B, Gudbjornsdottir S, on behalf of the Swedish National Diabetes Register. Albuminuria and renal function as predictors of cardiovascular events and mortality in a general population of patients with type 2 diabetes: A nationwide observational study from the Swedish National Diabetes Register. Diab Vasc Dis Res. 2013 Nov 1;10(6):520–9.

33. Nag S, Bilous R, Kelly W, Jones S, Roper N, Connolly V. All-cause and cardiovascular mortality in diabetic subjects increases significantly with reduced estimated glomerular filtration rate (eGFR): 10 years' data from the South Tees Diabetes Mortality study. Diabet Med J Br Diabet Assoc. 2007 Jan;24(1):10–7.

34. Bruno G, Cerutti F, Merletti F, Novelli G, Panero F, Zucco C, et al. Short-term mortality risk in children and young adults with type 1 diabetes: The population-based Registry of the Province of Turin, Italy. Nutr Metab Cardiovasc Dis. 2009 Jun;19(5):340–4.

35. Salinero-Fort MA, San Andrés-Rebollo FJ, de Burgos-Lunar C, Gómez-Campelo P, Chico-Moraleja RM, López de Andrés A, et al. Five-year incidence of chronic kidney disease (stage 3-5) and associated risk factors in a Spanish cohort: the MADIABETES Study. PloS One.

2015;10(4):e0122030.

36. Stadler M, Auinger M, Anderwald C, Kästenbauer T, Kramar R, Feinböck C, et al. Long-term mortality and incidence of renal dialysis and transplantation in type 1 diabetes mellitus. J Clin Endocrinol Metab. 2006 Oct;91(10):3814–20.

37. Penno G, Solini A, Bonora E, Fondelli C, Orsi E, Zerbini G, et al. HbA1c Variability as an Independent Correlate of Nephropathy, but Not Retinopathy, in Patients With Type 2 Diabetes. Diabetes Care. 2013 Aug 1;36(8):2301–10.

38. Retnakaran R, Cull CA, Thorne KI, Adler AI, Holman RR, UKPDS Study Group. Risk factors for renal dysfunction in type 2 diabetes: U.K. Prospective Diabetes Study 74. Diabetes. 2006 Jun;55(6):1832–9.

39. Zoppini G, Targher G, Chonchol M, Perrone F, Lippi G, Muggeo M. Higher HDL cholesterol levels are associated with a lower incidence of chronic kidney disease in patients with type 2 diabetes. Nutr Metab Cardiovasc Dis. 2009 Oct;19(8):580–6.

40. Looker HC, Colombo M, Hess S, Brosnan MJ, Farran B, Dalton RN, et al. Biomarkers of rapid chronic kidney disease progression in type 2 diabetes. Kidney Int. 2015 Oct;88(4):888–96.

41. Saulnier P-J, Gand E, Ragot S, Ducrocq G, Halimi J-M, Hulin-Delmotte C, et al. Association of serum concentration of TNFR1 with all-cause mortality in patients with type 2 diabetes and chronic kidney disease: follow-up of the SURDIAGENE Cohort. Diabetes Care. 2014 May;37(5):1425–31.

42. Pena MJ, Heinzel A, Heinze G, Alkhalaf A, Bakker SJL, Nguyen TQ, et al. A panel of novel biomarkers representing different disease pathways improves prediction of renal function decline in type 2 diabetes. PloS One. 2015;10(5):e0120995.

43. Rurali E, Noris M, Chianca A, Donadelli R, Banterla F, Galbusera M, et al. ADAMTS13 Predicts Renal and Cardiovascular Events in Type 2 Diabetic Patients and Response to Therapy. Diabetes. 2013 Oct 1;62(10):3599–609.

44. Jaziri R, Aubert R, Roussel R, Emery N, Maimaitiming S, Bellili N, et al. Association of ADIPOQ genetic variants and plasma adiponectin isoforms with the risk of incident renal events in type 2 diabetes. Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc. 2010 Jul;25(7):2231–7.

45. Bruno RM, Salvati A, Barzacchi M, Raimo K, Taddei S, Ghiadoni L, et al. Predictive value of dynamic renal resistive index (DRIN) for renal outcome in type 2 diabetes and essential hypertension: a prospective study. Cardiovasc Diabetol. 2015;14:63.

46. Gomez-Marcos MA, Recio-Rodríguez JI, Patino-Alonso MC, Agudo-Conde C, Gomez-Sanchez L, Rodriguez-Sanchez E, et al. Yearly evolution of organ damage markers in diabetes or metabolic syndrome: data from the LOD-DIABETES study. Cardiovasc Diabetol. 2011 Oct 14;10:90.

47. Sedaghat S, Mattace-Raso FUS, Hoorn EJ, Uitterlinden AG, Hofman A, Ikram MA, et al.

Arterial Stiffness and Decline in Kidney Function. Clin J Am Soc Nephrol CJASN. 2015 Dec 7;10(12):2190–7.

48. Mancini M, Masulli M, Liuzzi R, Mainenti PP, Ragucci M, Maurea S, et al. Renal Duplex Sonographic Evaluation of Type 2 Diabetic Patients. J Ultrasound Med. 2013 Jun 1;32(6):1033–40.

49. Petrica L, Vlad A, Gluhovschi G, Gadalean F, Dumitrascu V, Vlad D, et al. Glycated peptides are associated with the variability of endothelial dysfunction in the cerebral vessels and the kidney in type 2 diabetes mellitus patients: a cross-sectional study. J Diabetes Complications. 2015 Mar;29(2):230–7.

50. Stróżecki P, Kurowski R, Flisiński M, Stefańska A, Odrowąż-Sypniewska G, Manitius J. Advanced glycation end products and arterial stiffness in patients with diabetic nephropathy and patients with chronic kidney disease without diabetes. Pol Arch Med Wewnętrznej. 2013;123(11):609–16.

51. Naka KK, Papathanassiou K, Bechlioulis A, Kazakos N, Pappas K, Tigas S, et al. Determinants of vascular function in patients with type 2 diabetes. Cardiovasc Diabetol. 2012;11:127.

52. Theilade S, Lajer M, Persson F, Joergensen C, Rossing P. Arterial stiffness is associated with cardiovascular, renal, retinal, and autonomic disease in type 1 diabetes. Diabetes Care. 2013 Mar;36(3):715–21.

53. Theilade S, Lajer M, Hansen TW, Rossing P. Pulse wave reflection is associated with diabetes duration, albuminuria and cardiovascular disease in type 1 diabetes. Acta Diabetol. 2014 Dec;51(6):973–80.

54. Gordin D, Wadén J, Forsblom C, Thorn LM, Rosengård-Bärlund M, Heikkilä O, et al. Arterial stiffness and vascular complications in patients with type 1 diabetes: The Finnish Diabetic Nephropathy (FinnDiane) Study. Ann Med. 2012 Mar;44(2):196–204.

55. Hermans MMH, Henry R, Dekker JM, Kooman JP, Kostense PJ, Nijpels G, et al. Estimated glomerular filtration rate and urinary albumin excretion are independently associated with greater arterial stiffness: the Hoorn Study. J Am Soc Nephrol JASN. 2007 Jun;18(6):1942–52.

56. Tapp RJ, Shaw JE, Zimmet PZ, Balkau B, Chadban SJ, Tonkin AM, et al. Albuminuria is evident in the early stages of diabetes onset: Results from the Australian diabetes, obesity, and lifestyle study (AusDiab). Am J Kidney Dis. 2004 Nov;44(5):792–8.

57. al NR et. Diabetic kidney disease in Pima Indians. - PubMed - NCBI [Internet]. [cited 2016 Jul 29]. Available from: https://crypto.unil.ch/,DanaInfo=www.ncbi.nlm.nih.gov+pubmed?term=8422805

58. al BF et. The excess incidence of diabetic end-stage renal disease among blacks. A population-based study of potential explanatory factors. - PubMed - NCBI [Internet]. [cited 2016 Jul 29]. Available from: https://crypto.unil.ch/,DanaInfo=www.ncbi.nlm.nih.gov+pubmed?term=1433738

59. al SS et. Racial differences in the incidence and progression of renal diseases. - PubMed - NCBI [Internet]. [cited 2016 Jul 29]. Available from: https://crypto.unil.ch/,DanaInfo=www.ncbi.nlm.nih.gov+pubmed?term=1762285

60. Kohler KA, McClellan WM, Ziemer DC, Kleinbaum DG, Boring JR. Risk factors for microalbuminuria in black americans with newly diagnosed type 2 diabetes. Am J Kidney Dis. 2000 Nov;36(5):903–13.

61. Gelber RP, Kurth T, Kausz AT, Manson JE, Buring JE, Levey AS, et al. Association Between Body Mass Index and CKD in Apparently Healthy Men. Am J Kidney Dis. 2005 Nov;46(5):871–80.

62. Ejerblad E. Obesity and Risk for Chronic Renal Failure. J Am Soc Nephrol. 2006 Jun 1;17(6):1695–702.

63. Bakris GLM. Overview of diabetic nephropathy Uptodate, Waltham, MA. Uptodate Post TW Ed. 2014 Oct 20;

64. Penno G, Solini A, Bonora E, Fondelli C, Orsi E, Zerbini G, et al. Clinical significance of nonalbuminuric renal impairment in type 2 diabetes: J Hypertens. 2011 Sep;29(9):1802–9.

65. Pavkov ME, Mason CC, Bennett PH, Curtis JM, Knowler WC, Nelson RG. Change in the distribution of albuminuria according to estimated glomerular filtration rate in Pima Indians with type 2 diabetes. Diabetes Care. 2009 Oct;32(10):1845–50.

66. Conway BR, Manoharan D, Manoharan D, Jenks S, Dear JW, McLachlan S, et al. Measuring urinary tubular biomarkers in type 2 diabetes does not add prognostic value beyond established risk factors. Kidney Int. 2012 Oct;82(7):812–8.

11 Legends

11.1 Tables

11.2 Figures