**Supplementary Online Content**

**Supplementary Text**.Description of the four study cohorts

**Supplementary Table 1**. Biomarkers measured using targeted omics assays in the JDRF Biomarkers Consortium

**Supplementary Table 2**. Associations of clinical characteristics with rapid eGFR decline stratified by baseline eGFR and UACR in the JDRF Biomarkers Consortium

**Supplementary Text: Description of the four study cohorts**

*The Finnish Diabetic Nephropathy (FinnDiane) study cohort*

The FinnDiane study is a prospective nationwide multicenter study of more than 8,400 adults with T1D from 21 university and central hospitals, 33 district hospitals, and 26 primary health care centers across Finland and is the largest natural history study for T1D and its complications [1]. Patients are followed on a yearly basis and kidney function is measured via urine albumin excretion rates and eGFR measurements. The current study comprises 578 cases and controls studied between 1998 and 2011. Patients participated in the study during a regular visit to their attending physician during which detailed demographic and medical history data were collected with standardized questionnaires. Blood pressure was measured two times with 2-min intervals in the sitting position after an initial 10-min rest and the mean values were used for analysis. Hypertension was defined as > 130/85 mmHg over two readings or use of antihypertensive medication. HbA1c was measured with standard methods at the local centers; eGFR was estimated from serum creatinine values by the CKD-EPI equation [2]. Annual rate of eGFR change was calculated by fitting regression lines to serial eGFR measures for each patient. A participant was classified as having retinopathy if he/she received laser treatment. In a subset of 1,346 FinnDiane patients, that had been ETDRS graded from fundus photographs and ophthalmic records, we observed that 81.1% of laser-treated patients eventually were diagnosed with proliferative diabetic retinopathy [3]. This suggests that laser treatment could be used as a surrogate for severe retinopathy in FinnDiane. As the training of the Finnish ophthalmologists is uniform (one main instructor in the country the last 35 years) the indications for laser treatment at different centers are consistent.

All participants gave written consent prior to participation, and the study protocol was approved by the local ethics committees of each participating center. The study is performed in accordance with the Declaration of Helsinki as revised in the year 2000.

*The Steno study cohort*

The Steno Diabetes Center Copenhagen (SDCC) is specialized in the treatment, research and prevention of diabetes and in the education of healthcare professionals [4]. It is Scandinavia’s largest diabetes clinic (www.sdcc.dk).

The current study cohort is comprised of Caucasian adults (age ≥18 years) with T1D attending the SDCC out-patient clinic. Their follow up time ranges from 4 to 10 years (median 4.65 years). The SDCC T1D sample may be sub-grouped on the basis of their baseline examination dates. The first set of T1D cases was enrolled between May 1995 to April 1996 while participating in the Low Protein Diet (LPD) study with a T1D onset of at least 10 years [5]. The second set of T1D cases were enrolled in 2004 for a study of biomarkers related to nephropathy, while the last set of T1D cases were enrolled between 2009-2011 and participated in a study of biomarkers of nephropathy and arterial stiffness [6,7].

Patient demographics, biochemical measurements, and medical history data were collected at each follow-up visit. Blood pressure measures were recorded with either a validated tonometric device (BPro; HealthStats, Singapore), or using the Hawksley Random Zero Sphygmomanometer, with a mean of at least two measures [5,7]. Hypertension was defined as use of antihypertensive medication. High-performance liquid chromatography (Bio Rad Laboratories, Munich, Germany) was used to estimate HbA1c (normal range: 4.1-6.4%) and an enzymatic method (Hitachi 912; Roche Diagnostics, Mannheim, Germany) was used to measure serum creatinine concentrations [7]. Urinary albumin excretion ratio (UAER) was measured in 24-h sterile urine collections by enzyme immunoassay; eGFR was calculated using the CKD-EPI creatinine equation. The rate of decline in kidney function was analyzed with regression lines for eGFR over the follow-up period using all measurements of eGFR during the study period. Retinopathy was assessed via retinal photographs taken during regular ophthalmologic examinations. All participants gave written informed consent, and the study was approved by the Danish National Ethics committee. A total of 362 Steno cases and controls are included in the current analysis.

*Epidemiology of Diabetes Complications (EDC) study cohort*

The EDC is a prospective historical cohort study based on incident cases of childhood onset (<17 years) T1D, diagnosed or seen within one year of diagnosis (1950-80) at Children’s Hospital of Pittsburgh [8]. The cohort, which has been shown to be epidemiologically representative of the Allegheny County, Pennsylvania, T1D population, was first assessed for the EDC study between 1986 and 1988 (mean participant age and diabetes duration were 28 and 19 years, respectively) [9]. Subsequently, biennial examinations were conducted for 10 years, with a further detailed examination at 18 and 25 years from enrollment. All EDC study participants provided informed consent, and all study procedures were approved by the University of Pittsburgh Institutional Review Board (IRB).

Demographic, health, self-care and medical history data were collected at each follow-up. Blood pressure was measured with a random zero sphygmomanometer, after a five-minute rest and hypertension was defined as > 140/90 mmHg or use of antihypertensive medication. Automated high-performance liquid chromatography (Diamat; Bio-Rad, Hercules, CA) was performed for Hemoglobin A1c (HbA1c) [10]. Glomerular filtration rate was estimated by the CKD-EPI creatinine equation. Retinopathy was classified according to the modified Airlie House classification; the methodology has been described in detail elsewhere [11]. Proliferative retinopathy was defined as a grade of ≥60 in at least one eye or a history of panretinal photocoagulation for proliferative diabetic retinopathy. To achieve reasonable temporal comparability to the other cohorts, the current study used the years 1996-98 to define the baseline measure; 146 such participants (cases and controls) met the criteria and are included in the present study. Annual rate of eGFR change was calculated using the difference between the first (1996-98 exam) and last available eGFR (2001-03 or 2004-06 exam) and dividing by the number of years between the two measures.

*Coronary Artery Calcification in Type 1 Diabetes (CACTI) study cohort*

The CACTI study enrolled 652 adults ranging in age from 19-56 years between 2000-2002 into a prospective cohort study designed to examine cardiovascular and related complications of T1D [12]. All participants were free of diagnosed cardiovascular disease, and did not have a cardiovascular event (myocardial infarction, angioplasty or coronary artery bypass graft). Participants were either diagnosed with T1D before the age of 30, or if diagnosed over age 30, they had positive autoantibodies or a clinical course consistent with T1D. All were on insulin within a year of diagnosis and at the time of enrollment. Participants have been followed longitudinally at three and six years for complications, including diabetic nephropathy. All study participants provided informed consent, and the study was approved by the Colorado Multiple IRB.

Demographic, health, self-care and medical history data were collected at baseline and at three subsequent follow-up examinations. Blood pressure was measured three times via random zero sphygmomanometer, after a five-minute rest, and the second and third measurements were averaged. Hypertension was defined as >140/90 mmHg or use of antihypertensive medication. HbA1c was assayed by high performance liquid chromatography (BioRad Variant). A participant was classified as having retinopathy if he/she received laser treatment. Glomerular filtration rate was estimated by the CKD-EPI creatinine equation. Average annual decline in eGFR was calculated as absolute change in eGFR from the baseline exam to the last visit in the study divided by the number of years between these two visits. The current analysis is based on 344 patients (with fast (cases) or slow (controls) kidney function decline) from the CACT1 cohort.

**Supplementary Table 1: Biomarkers measured using targeted omics assays in the JDRF Biomarkers Consortium**

|  |  |  |
| --- | --- | --- |
| **Project** | **Measured biomarkers** | |
| Metabolomics | 2-Methyl acetoacetate  2-Hydroxybutyrate  2-Hydroxyglutaric acid  2-Hydroxyisovaleric acid  2-Ketoadipic acid  2-Ketoglutaric acid  2-Ethyl-3-hydroxyproprionate  3-Hydroxyisobutyrate  3-Hydroxyisovalerate  3-Hydroxypropionate  3-Hydroxyadipic acid  3-Hydroxybutyric acid  3-Hydroxyglutaric acid  3-Methyladipic acid  3-Methylcrotonylglycine  3-Methylglutaconic acid  4-Aminobutyric acid  4-Hydroxyhippurate  4-Hydroxyphenyllactic acid  Acetoacetic acid  Aconitic acid  Adipic Acid | Citric acid  Ethylmalonic acid  Fumaric acid  Glycolic acid  Glyoxylic acid  Hippuric acid  Homovanillic acid  Hydrocinnamic acid  Isocitric acid  Lactic acid  Malic acid  Methylsuccinic acid  N-Acetylaspartate  N-Acetyl-L-tyrosine  Palmitic acid  Pyruvic acid  Stearic acid  Succinic acid  Tiglylglycine  Uracil  Uric acid |
| Lipidomics\* | Free fatty acids  Lysophosphatidylcholines  Sphingomyelins  Phosphatidylcholines  Triglycerols | Diacylglycerols  Cholesteryl esters  Phosphatidylethanolamines  L-carnitine  Acylcarnitines |
| Proteomics | Podocalyxin Renin receptor Urokinase-type plasminogen activator Epidermal growth factor Collagen alpha-1(I) chain Collagen alpha-1(III) chain Intracellular adhesion molecule 1 Cathepsin D Matrix metalloproteinase 7 Cytosolic non-specific dipeptidase 2 | Insulin-like growth factor binding protein 2 Insulin-like growth factor binding protein 3 Insulin-like growth factor binding protein 7 Vascular cell adhesion protein 1 Connective tissue growth factor Syndecan-4 Aquaporin-2 Selenoprotein P Urokinase receptor Endothelial cell-selective adhesion molecule |

\*326 lipid species measured across the listed lipid classes.

**Supplementary Table 2: Associations of clinical characteristics with rapid eGFR decline stratified by baseline eGFR and UACR in the JDRF Biomarkers Consortium**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Baseline eGFR** | | | **Baseline UACR** | | | **Combination of 90 < eGFR ≤ 120 and normoalbumin- uria\***  N (cases) =  434 (140) |
|  | **60 < eGFR ≤90 ml/min/1.73m2**  N (cases) = 511 (129) | **90 < eGFR ≤ 120 ml/min/1.73m2**  N (cases) = 638 (236) | **120 < eGFR ≤150 ml/min/1.73m2**  N (cases) =  166 (117) | **Macro: > 300 mg/g**  N (cases) = 143 (99) | **Micro: >30, < 300 mg/g**  N (cases) =  323 (134) | **Normo: < 30 mg/g**  N (cases) =  881 (269) |
| Age  (per 10 years) | 0.99  (0.71, 1.14) | 0.82  (0.66, 1.03) | 0.80  (0.44, 1.45) | 1.12  (0.68, 1.89) | 0.72  (0.55, 0.93) | 0.91  (0.74, 1.11) | 0.79  (0.60, 1.04) |
| Sex  (Ref: female) | 1.04  (0.64, 1.68) | 0.81  (0.56, 1.15) | 0.47  (0.21, 1.02) | 1.63  (0.71, 3.81)c | 1.25  (0.77, 2.05) | 0.58  (0.41, 0.81) | 0.68  (0.44, 1.05) |
| Diabetes duration  (per 10 years) | 1.16  (0.93, 1.47) | 1.31  (1.08, 1.60) | 1.48  (0.82, 2.73) | 0.93  (0.53, 1.61) | 1.25  (0.95, 1.66) | 1.34  (1.13, 1.61) | 1.30  (1.04, 1.64) |
| HbA1c  (per 1%) | 1.21  (0.97, 1.53) | 1.26  (1.10, 1.45) | 0.98  (0.77, 1.25) | 1.66  (1.24, 2.29) | 1.36  (1.14, 1.65) | 1.08  (0.94, 1.24) | 1.22  (1.02, 1.46) |
| Mean arterial pressure  (per 10 mmHg) | 1.20  (0.96, 1.49) | 1.07  (0.90, 1.27) | 0.98  (0.65, 1.49) | 1.05  (0.74, 1.49) | 1.14  (0.91, 1.45) | 1.07  (0.91, 1.26) | 1.10  (0.89, 136) |
| UACR (per doubling) | 1.39  (1.27, 1.53) | 1.14  (1.04, 1.24) | 1.10  (0.91, 1.36) | 1.60  (1.07, 2.46) | 1.32  (1.03, 1.70) | 0.98  (0.83, 1.16)d | 1.06  (0.85, 1.32) |
| eGFR  (per 10 ml/min/1.73m2) | 0.79  (0.61, 1.03) | 1.75  (1.38, 2.24) | 1.97  (1.09, 3.79) | 1.15  (0.99, 1.35) | 1.11  (0.99, 1.24) | 1.80 (1.60, 2.04) | 1.83  (1.37, 2.47) |

Cell contents are odds ratios (95% CI) adjusted for age, sex, diabetes duration, and baseline HbA1c, MAP, log2(UACR), and eGFR.

\*Other combinations of UACR and eGFR strata had small cell-sizes, and hence were not evaluated.

The following interactions were significant at a p < 0.10:

* eGFR(90,120]\*covariate interaction significant for log2(UACR) (p=0.002), baseline eGFR (P < 0.001); Reference category: eGFR[60,90]
* eGFR(120,150]\*covariate interaction marginally significant for sex (p=0.09); significant for log2(UACR) (p=0.04), baseline eGFR (P < 0.01); Reference category: eGFR(60,90
* Macroalbuminuria\*covariate interaction significant for sex (p=0.02), HbA1c (p=0.01), log2(UACR) (p=0.03), baseline eGFR (p < 0.001); Reference category: Normoalbuminuria group
* Microalbuminuria\*covariate interaction significant for sex (p=0.01), HbA1c (p=0.047), log2(UACR) (p = 0.048), baseline eGFR (p < 0.001)

**Additional References for Supplementary Material**

1. Thorn LM, Forsblom C, Fagerudd J, et al. Metabolic syndrome in type 1 diabetes: Association with diabetic nephropathy and glycemic control (the FinnDiane study). Diabetes Care. 2005;28(8):2019-2024. doi:10.2337/diacare.28.8.2019

2. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-612. doi:10.4172/2161-0959.1000264

3. Hietala K, Wadén J, Forsblom C, et al. HbA1c variability is associated with an increased risk of retinopathy requiring laser treatment in type 1 diabetes. Diabetologia. 2013;56(4):737-745. doi:10.1007/s00125-012-2816-6

4. Ferreira I, Hovind P, Schalkwijk CG, Parving HH, Stehouwer CDA, Rossing P. Biomarkers of inflammation and endothelial dysfunction as predictors of pulse pressure and incident hypertension in type 1 diabetes: a 20 year life-course study in an inception cohort (a STENO group). Diabetologia. 2018;61(1):231-241. doi:10.1007/s00125-017-4470-5

5. Hansen HP, Tauber-Lassen E, Jensen BR, Parving HH. Effect of dietary protein restriction on prognosis in patients with diabetic nephropathy. Kidney Int. 2002;62(1):220-228. doi:10.1046/j.1523-1755.2002.00421.x

6. Rossing K, Mischak H, Dakna M, et al. Urinary Proteomics in diabetes and CKD. J Am Soc Nephrol. 2008;19(7):1283-1290. doi:10.1681/ASN.2007091025

7. 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;36(3):715-721. doi:10.2337/dc12-0850

8. Orchard TJ, Dorman JS, Maser RE, et al. Prevalence of complications in IDDM by sex and duration: Pittsburgh Epidemiology of Diabetes Complications study II. Diabetes. 1990;39(9):1116 LP - 1124. doi:10.2337/diab.39.9.1116

9. Wagener DK, Sacks JM, LaPorte RE, MaCgregor JM. The Pittsburgh study of insulin-dependent diabetes mellitus: risk for diabetes among relatives of IDDM. Diabetes. 1982;31(2):136 LP - 144. doi:10.2337/diab.31.2.136

10. The hypertension detection and follow-up program: Hypertension detection and follow-up program cooperative group. Prev Med. 1976;5(2):207-215.

11. Johnson LN, Diehl ML, Hamm CW, Sommerville DN, Petroski GF. Differentiating optic disc edema from optic nerve head drusen on optical coherence tomography. Arch Ophthalmol. 2009;127(1):45-49. doi:10.1001/archophthalmol.2008.524

12. Hamman RF, Rewers M, Ehrlich J, et al. Effect of type 1 diabetes on the gender difference in coronary artery calcification: a role for insulin resistance?: the Coronary Artery Calcification in Type 1 Diabetes (CACTI) study. Diabetes. 2003;52(11):2833-2839. doi:10.2337/diabetes.52.11.2833