No prognostic role of a GWAS-derived genetic risk score in renal outcomes for patients from French cohorts with type 1 and type 2 diabetes

Diabetic nephropathy (DN) is a complex disease characterized by the interaction of genetic and environmental factors, as suggested by the interaction between ACE insertion/deletion (I/D) polymorphisms and blood glucose control in the risk for DN progression [1]. Family-based studies have suggested the role of genetic factors in the development of the disorder in diabetes patients [2,3], and recent genome-wide association studies (GWAS) have identified several single-nucleotide polymorphisms (SNPs) associated with chronic kidney disease (CKD) [4].

While the risk factors for renal impairment are multiple, the currently available genetic data have not been fully exploited. The hypothesis according to which genetic information could enhance the prediction of CKD risk in diabetes patients has yet to be tested, particularly in a real-life setting, as suggested by the effects of two GWAS-identified SNPs [5]. For this reason, our present study has assessed the value of CKD-associated SNPs, selected from the two seminal papers, to evaluate the risk of renal function decline in two French prospective cohorts of diabetes patients, one with type 2 diabetes (T2D) and the other with proteinuric type 1 diabetes (T1D).

For T2D, the *Survie, diabète de type 2 et génétique* (SURDIAGENE; Survival, Type 2 Diabetes and Genetics) study was used; this was a single-centre prospective hospital-based cohort study (CHU Poitiers) with consecutive recruitment aiming to identify the genetic and environmental determinants of the micro- and macrovascular complications of T2D [6]. The institutional ethics committee (CPP Ouest 3) approved the study protocol, and written consent was obtained from every participant.

For T1D, the previously reported French cohorts of the Juvenile Diabetes Research Foundation (JDRF) Diabetic Nephropathy Collaborative Research Initiative [7] were used. That study evaluated factors associated with renal function decline in T1D patients with clinical proteinuria recruited from five French cohorts.

The present work focused on patients with CKD stages 1–4 at baseline, defined as a glomerular filtration rate (GFR) $\geq$ 15 mL/min/1.73 m^2 regardless of urinary albumin in T2D, and in proteinuric patients with T1D.

A total of 18 SNPs, identified by the CKDGen consortium to be associated with renal function or CKD grade 5, were selected (Table S1; see supplementary materials associated with this article online) [4,5]. The SNPs were genotyped in a single batch by the KASPar assay system in SURDIAGENE patients with T1D, using the HumanCoreExome-12 v1.0 BeadChip (Illumina, San Diego, CA, USA). A genetic risk score (GRS) was established by summing up the number of at-risk alleles, but because of imperfect call rates, the sums were divided by the number of typed alleles per individual. Patients with call rates < 90% for more than two SNPs were excluded from the analysis (out of 1381 SURDIAGENE participants, 13 had no genotype and 52 had incomplete genetic information). Expressed as a percentage, the GRS has a theoretical value of 0–100 (where 0 indicates no risk alleles and 100 indicates all risk alleles of the tested SNPs). A weighted score was used for the sensitivity analysis.

Abbreviations: BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; CKD-EPI, Chronic Disease Kidney Epidemiology Collaboration; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; GRS, genetic risk score; GWAS, genome-wide association studies; HbA_{1c}, glycated haemoglobin; HR, hazard ratio; IQR, interquartile range; SBP, systolic blood pressure; SNP, single-nucleotide polymorphism; SURDIAGENE, *Survie Diabète de type 2 et Génétique*; uACR, urinary albumin-to-creatinine ratio; UAE, urinary albumin excretion.

The main study endpoint was a renal event, defined as the first event to appear with doubling of serum creatinine for > 1 month and end-stage renal disease necessitating renal replacement therapy. Secondary endpoints consisted of the estimated GFR (eGFR) trajectory, built by at least three eGFR determinations during follow-up, and all-cause deaths. Follow-up was considered the time from patient inclusion to either the appearance of a renal event or up to 2013.

Qualitative variables were presented as numbers and percentages and compared with the Chi^2 or Fisher's exact test. Quantitative variables were expressed as means ± standard deviation (SD) or medians (interquartile range, IQR) according to their distribution. Student's or analysis of variance (ANOVA) tests were used to compare linear variables; Wilcoxon or Kruskal–Wallis tests allowed comparisons of the distributions of non-linear quantitative variables.

Patients' GRS distributions were split into tertiles. Due to the large number of ex aequo results, however, these tertiles comprised different numbers of patients: the lowest had a low GRS (< 48%); the middle tertile had an intermediate GRS ($\geq$ 48–56%); and the highest tertile had a high GRS (> 56%). A univariate semiparametric Cox model was constructed to evaluate the risk of renal events over time according to GRS group and clinical variables. Results were given as hazard ratios (HRs) and their confidence intervals (CIs).

A fixed-effects model was used for meta-analysis, and mixed-effects (fixed- and random-effects) models were used for the eGFR trajectory during follow-up. A random constant and a random slope were systematically inserted into the models to integrate individual variations at the beginning of follow-up and over time [7].

SAS version 9.3 (SAS Inc., Cary, NC, USA) and R version 3.2.1 (www.R-project.org/accessed Feb 4, 2016) software were used to compile the statistics. Quanto version 18.2 software was used for power calculations. All analyses were carried out using a *P* value of 0.05.

Our study population included 1316 patients with T2D and 303 with T1D. For the eGFR trajectory, 23,179 and 6312 determinations in 1120 and 303 patients with T2D and T1D, respectively, were applied. The mean ± SD GRS was 51.3 ± 7.76 and 51.4 ± 4.44 in patients with T2D and T1D, respectively.

At baseline, GRS did not differ according to CKD stage (Tables S2 and S3; see supplementary materials associated with this article online). The relationship between GRS divided into tertiles and baseline data is summarized in Table S4 (see supplementary materials associated with this article online). During follow-up (median durations of 70 and 99 months for T2D and T1D, respectively), 80 and 120 renal events were seen in patients with T2D and T1D, respectively, translating into an incidence of 1.1% person-years (95% CI: 0.8–1.3%) and 4.3% person-years (95% CI: 3.6–5.1%), respectively. Patients' characteristics according to the presence, or not, of a renal event during follow-up are described in Table 1. The risk of renal events did not differ according to GRS (HR: 1.08, 95% CI: 0.82–1.44; *P* = 0.58 *vs* HR: 1.65, 95% CI: 0.17–15.71; *P* = 0.66 for each 10% increase in GRS in patients with T2D and T1D, respectively). This did not change when taking the competing risk of death into account (data not shown). In the meta-analysis, the risk of renal events likewise did not differ with each 10% increase in GRS: HR: 1.09, 95% CI: 0.82–1.44; *P* = 0.56, *P* = 0.72 for heterogeneity.

In addition, no significant difference in renal-event-free Kaplan–Meier survival curves was found according to tertiles of GRS in patients with T2D and T1D (log-rank = 0.88, *P* = 0.64 and log-rank = 3.8, *P* = 0.15, respectively; Figs. S1 and S2; see supplementary materials associated with this article online). Also, no SNP considered on its own was associated with risk of renal events

Table 1
Characteristics of patients at baseline according to the presence, or not, of a renal event during follow-up.

Characteristics	Type 2 diabetes			Type 1 diabetes		
	Renal event ($n = 80$)	No event ($n = 1236$)	P	Renal event ($n = 120$)	No event ($n = 183$)	P
Men (n [%])	61 (76%)	697 (56%)	**0.0005**	67 (56%)	112 (61%)	0.4179
Age (years)	64 ± 10	65 ± 11	0.6545	42 ± 10	43 ± 12	0.3073
Body mass index (kg/m^2)	31 ± 7	31 ± 6	0.5214	24 ± 4	24 ± 3	0.1290
Active smoking (n [%])	9[d] (11%)	132[d] (11%)	0.9085	44 (37%)	58 (32%)	0.5489
Diabetes duration (years)	16 ± 10	14 ± 10	0.1223	27 ± 9	26 ± 10	0.8482
HbA_{1c} (%)	8.1 ± 2.0	7.8 ± 1.5	0.0727	8.8 ± 1.8	8.8 ± 1.9	0.9363
Serum creatinine (μmol/L)	125 (98)	81 (30)	< **0.0001**	124 (72)	97 (37)	< **0.0001**
eGFR (mL/min/1.73 m^2)	54 ± 28	75 ± 22	< **0.0001**	61 ± 28	76 ± 26	< **0.0001**
uACR (mg/mmol)	89.8 (202.2)	2.6 (9.3)	< **0.0001**	–	–	
UAE (mg/24 h)	–	–		928 (2035.8)	426 (601.5)	< **0.0001**
Albuminuria stage			< **0.0001**			0.0948
Normal to mildly increased[a]	12 (15%)	498 (45%)		11 (10%)	11 (6%)	
Moderately increased[b]	12 (15%)	402 (37%)		25 (22%)	59 (33%)	
Severely increased[c]	55 (70%)	200 (18%)		78 (68%)	109 (61%)	
SBP (mmHg)	142 ± 22	132 ± 17	< **0.0001**	141 ± 19	141 ± 19	**0.0019**
DBP (mmHg)	76 ± 13	72 ± 11	**0.0010**	84 ± 11	80 ± 10	**0.0043**
Genetic risk score (%)	52.0 ± 7.3	51.3 ± 7.8	0.4403	51.8 ± 8.0	51.1 ± 8.1	0.4588

Quantitative variables are expressed as means ± SD or medians (IQR); HbA_{1c}: glycated haemoglobin; eGFR: estimated glomerular filtration rate; uACR: urinary albumin-to-creatinine ratio; UAE: urinary albumin excretion; SBP/DBP: systolic/diastolic blood pressure. Bold values correspond to statistically significant differences.
[a] uACR < 3 mg/mmol or UAE < 30 mg/24 h.
[b] uACR 3–29 mg/mmol or UAE 30–299 mg/24 h.
[c] uACR ≥ 30 mg/mmol or UAE ≥ 300 mg/24 h.
[d] Missing data for 18 patients in non-renal event groups.

after correcting for multiple testing (Tables S5 and S6; see supplementary materials associated with this article online).

During follow-up, there were 383 and 77 deaths in patients with T2D and T1D, respectively. The non-adjusted HR of each 10% increase in GRS for all-cause death was non-significant (NS) in T2D and T1D patients (HR: 0.96, 95% CI: 0.84–1.09; $P = 0.53$ and HR: 0.34, 95% CI: 0.02–6.09; $P = 0.46$, respectively). These results remained unchanged for renal outcomes and all-cause deaths when considering imputed SNPs using their average genotype values (data not shown). In the meta-analysis, the non-adjusted HR of each 10% increase in GRS for all-cause death was NS: HR: 0.96, 95% CI: 0.84–1.09; $P = 0.52$, $P = 0.48$ for heterogeneity.

Power calculations to ascertain differences in GRS between patients with and without renal events are presented in Table S7 (see supplementary materials associated with this article online). The power was 98% for a difference of 5% (two at-risk alleles) in GRS for renal events in T2D *vs* 100% in T1D. On the other hand, the power to identify a difference of 2.8% (one at-risk allele) in GRS was 63% for renal events in T2D and 99% in T1D.

On analyzing eGFR trajectory in a mixed-effects linear model, GRS was not significantly related to eGFR trajectory in either T2D or T1D ($P = 0.49$ or $P = 0.13$, respectively). On pooling both T2D and T1D patients, every 10% increase in GRS was associated with an NS effect on eGFR trajectory ($P = 0.43$). Also, no SNP considered on its own was associated with eGFR trajectory (Tables S5 and S6; see supplementary materials associated with this article online), whereas the clinical covariates of age, eGFR and urinary albumin-to-creatinine ratio (uACR) were (data not shown). Weighting the GRS did not modify our results.

In our cohorts of T2D and T1D patients, no single SNP or GRS-based on the 18 SNPs identified by the CKDGen consortium was of prognostic value for either renal outcomes or all-cause death, whereas traditional variables such as baseline uACR and baseline eGFR were strongly associated with risk of renal events.

To our knowledge, the present study is the first to apply a GRS-based approach to renal risk in diabetes patients in a real-life setting. Our hypothesis was that the use of a GRS-based on the number of at-risk alleles in an individual would yield more information than clinical scores alone. However, none of the tested SNPs was relevant to the renal prognosis, and no SNP on its own was associated with renal function decline.

Using a similar approach, one of the first predictive reports to focus on T2D and to assess a GRS including 18 SNPs associated with T2D risk was the Framingham study [8]. However, adding the GRS to the classic risk factors did not significantly alter their ability to determine diabetes risk, and any effects were most likely too small to yield any interesting individual findings. Our present results also suggest that supplementary genetic data do not effectively help to 'individualize' the risk of renal function decline.

One report from the CKDGen consortium suggested that the effects of many CKD/eGFR-related SNPs found in the general population would be similar in any general population and in diabetes patients [9]. A set of 13 SNPs of the 18 selected for our study yielded similar effects sizes in both the diabetes and non-diabetes groups. Thus, this work helps to rule out the hypothesis that the SNPs selected to establish the GRS were not relevant to a diabetes population.

Nevertheless, some study limitations must be acknowledged. Our sample size was limited despite its reasonable *a priori* statistical power. Recruitment was mainly hospital-based, leading to some caveats in generalizing our present findings. Finally, other computing strategies could have been applied to derive the GRS. However, no indications emerged to support the selected SNPs, leaving room for improvement in precision medicine using genomic data. Another caveat is that our study focused solely on loci identified by two seminal reports, and did not include all the SNPs available in the literature to date.

In conclusion, a GRS-based on 18 GWAS-derived SNPs does not allow clinically relevant prediction of the risk of chronic renal failure in patients with either T2D or T1D.

Funding

The SURDIAGENE study was supported by grants from the French Ministry of Health (PHRC-Poitiers 2004 & PHRC-IR 2008), *Association française des diabétiques* (Research Grant 2003), and Groupement pour l'Etude des Maladies Métaboliques et Systémi-

ques (GEMMS Poitiers, France). The work in type 1 diabetes patients was made possible thanks to the support of JDRF grant 17-2013-8.

Availability of data and materials

Our present data can easily be accessed on simple request to the corresponding author from bona fide researchers and/or clinicians.

Authors' contributions

P.B., B.G. and S.H. researched data, wrote the manuscript and contributed to the discussion. E.G. researched data, performed statistical analysis and contributed to the discussion. D.-A.T. and B.G. researched data and performed statistical analysis. All authors contributed to the discussion. S.H. is the guarantor of this work and, as such, had full access to all the data in the study, and takes responsibility for the integrity of the data and accuracy of the data analysis.

Consent for publication

Not applicable.

Ethics approval and consent to participate

All participants in this research signed an informed consent form. Ethics committees approved the designs of all the different studies.

Disclosure of interest

P.B., B.G., E.G., J.M.H., E.F., C.H.D., P.L., P.Z., S.R., D.A.T. declare that they have no competing interest.

P.J.S. has received travel grants from Novo Nordisk, Servier, Takeda, Roche diagnostic and Dinno Santé.

G.D. has received Speaker's and/or consulting fees: Astra Zeneca, Bayer, Biotronik, BMS, Sanofi and Travel grants: Astra Zeneca, Biotronik.

D.M. has received honorarium or speaking fees from BMS, Pfizer, MSD and Bayer.

V.R. has received travel grants for congress from Bayer, GSK, Novo, Lilly, Pfizer, Takeda, Scherring-Plough, MSD, Novartis, and Abbott.

R.R. has been in advisory panel for AstraZeneca, Abbvie, Sanofi, MSD, Eli Lilly, Janssen, Novo Nordisk, and Physiogenex; a speaker for Bayer and Servier; has received research funding and provided research support to Danone Research, Amgen, Sanofi, and Novo Nordisk.

P.S. has received Congress travel grant from Servier.

M.M. has received honoraria and grants from Abbott, AstraZeneca, Eli Lilly, Merck, Novo-Nordisk, Sanofi, and Servier.

S.H. has served as a consultant and/or on advisory panels for AstraZeneca/Bristol Myers Squibb, has received honorarium or speaking fees from AstraZeneca/Bristol Myers Squibb, Abbott, Boehringer Ingelheim, Eli-Lilly, Janssen, Merck Sharpe Dome, Novartis, Novo Nordisk, Sanofi, Servier and Takeda, has received research grants from Abbott and Takeda, and has received travel grants from Janssen, AstraZeneca/Bristol Myers Squibb, Merck Sharpe Dome, Sanofi.

Acknowledgements

All patients included and followed in our cohorts are warmly thanked for their kind participation in this research. Their general practitioners are acknowledged for their help in collecting clinical information. The authors acknowledge the technical assistance of all the staff from the Department of Endocrinology and Diabetology (recruitment), and Sonia Brishoual (CRB BB0033-00068) and the staff of INSERM CIC 1402 (data management). Gérard Mauco (Department of Biochemistry, CHU Poitiers) and Thierry Hauet (INSERM U1082, CHU Poitiers) are acknowledged for helping with biological determinations. Jeffrey Ashram edited the English manuscript. D.-A.T. and B.G. are partially supported by Institute for Cardiometabolism and Nutrition (ICAN; ANR-10-IHU-05).

Thanks also go to the French JDRF Diabetic Nephropathy Collaborative Research Initiative (the search for genes determining time to onset of ESRD in T1D patients with proteinuria).

Cohorts: GENESIS & GENEDIAB: M. Marre (Bichat, Paris); Toulouse Diabetes Center (P. Gourdy, Toulouse); Corbeil-Essonnes Diabetes Center (G. Charpentier, Corbeil-Essonnes); Paris Saint Louis Diabetes Center (J.F. Gautier, Paris Lariboisière); Nantes Diabetes Center (B. Cariou, Nantes); Poitiers Diabetes Center (S. Hadjadj, Poitiers).

Biological sample management: GENEDIAB & GENESIS, INSERM U695, Paris (M. Marre, N. Bellili); Corbeil-Essonnes Diabetes Center, UMR 8090, Lille (P. Froguel, S. Gagné); Nantes–Paris St Louis–Toulouse Diabetes Center–ISIS Study Kremlin Bicêtre, INSERM U 986 (P. Bougnères, D. Fradin, S. Le Fur); Poitiers Diabetes Center, INSERM CIC1402 & CRB 0033-00068, Poitiers (S. Hadjadj, P.J. Saulnier, S. Brishoual).

Appendix A. Supplementary data

Supplementary materials (Figs. S1–S2 and Tables S1–S7) associated with this article can be found at http://www.sciencedirect.com at https://doi.org/10.1016/j.diabet.2018.01.016.

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Received 5 September 2017
Received in revised form 29 November 2017
Accepted 29 January 2018
Available online 10 February 2018

https://doi.org/10.1016/j.diabet.2018.01.016

Excess foetal growth and glycaemic control in type 1 diabetes and pregnancy

Despite advances in diabetes care for women with type 1 diabetes (T1D) in pregnancy, the incidence of large-for-gestational-age (LGA) neonates (birth weight > 90th centile for gestational age and gender) and macrosomia (birth weight > 4,000 g) remains high. Recent studies have demonstrated rates of LGA between 40% and 80% in T1D pregnancy [1,2], and hyperglycaemia, glycaemic variability and maternal weight gain have all been shown to contribute towards excess foetal growth [3,4]. As a result of the increased tendency towards larger babies in T1D pregnancy, these women are advised to have regular ultrasound scans to monitor foetal growth in the third trimester and to have early term delivery [5].

Several studies have examined the relationship between maternal glycaemic control and acceleration of foetal growth in T1D pregnancy, with conflicting results. All of the studies observed that LGA neonates demonstrate excess foetal growth on ultrasound scans as early as the mid second trimester; however, this was not associated with maternal glycaemic control in two studies [6,7] and was associated with maternal glycaemic control in the first and/or second trimester in two other studies [8,9].

Therefore, the aim of the present study was to determine the relationship between glycaemic control throughout pregnancy in women with T1D and foetal abdominal circumference (AC) as a marker of foetal growth.

We conducted a retrospective cohort study in women aged greater than 18 years with T1D and a singleton pregnancy who attended the multi-disciplinary specialist obstetric clinic (SOC) at Royal North Shore Hospital, a large, tertiary referral hospital in Sydney, Australia, from January 2012 to June 2017. Approval for this study was obtained from the Northern Sydney Local Health District Human Research Ethics Committee (Reference No. LNR/16/HAWKE/191) and the study was carried out in keeping with the STROBE statement for cohort studies.

Data were extracted from patient electronic medical records and included maternal demographics (age, BMI recorded at the first visit to the antenatal clinic, parity, duration of diabetes, mode of insulin therapy) and the following outcomes: maternal outcomes – mode of delivery and complications in delivery, and perinatal outcomes – birth weight, gestational age at delivery, respiratory distress, neonatal hypoglycaemia, jaundice and neonatal intensive care unit (NICU) admission. In addition, ultrasound data including AC were recorded at 22–26, 27–30, 31–33 and 34–37 weeks' gestation during routine foetal growth assessment scans.

The online intergrowth-21st project foetal AC centile calculator was used to assess foetal size relative to population standards and was expressed as AC z-score. Similarly, the online intergrowth-21st project birth weight centile calculators were used to calculate LGA neonates. These centile calculators were chosen as they represent international standards for foetal growth and neonatal size across a multi-ethnic cohort of women [10].

Using the values for foetal AC reported in a previous study of T1D in pregnancy [6], with α 0.05 and power 0.9, a sample size of 13 per group is required to see a significant difference in foetal growth. Differences between groups were compared using Student's *t*-test or the Mann–Whitney test for parametric and non-parametric data, respectively, with Bonferroni correction for multiple comparisons. Fisher's exact test was used to analyse categorical data and Spearman's correlation was carried out to determine the association between AC centile and HbA1c. Receiver operator characteristic (ROC) curves were used to determine the ability of HbA1c at each time point to identify LGA neonates. The optimal HbA1c value for predicting LGA neonates was determined from the ROC curve using Youden's statistic. Statistical analyses were done using GraphPad Prism Version 7 and a P value < 0.05 was considered statistically significant.

Seventy women with T1D in singleton pregnancy were identified. For women with more than one pregnancy during the study time-period ($n = 10$), the first pregnancy was included.