A panel of novel biomarkers representing different disease pathways improves prediction of renal function decline in T2D

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SysKid Collaborative Project
Systems Biology towards Novel Chronic Kidney Disease Diagnosis and Treatment

Introduction

Given the complexity of the multiple pathophysiological processes in type 2 diabetes mellitus (T2D), it is unlikely that a single biomarker may possess sufficient diagnostic and prognostic power. Alternatively, a combination of biomarkers that capture the different pathways of renal damage compensates for the variability of individual markers and may provide a more realistic picture of the actual pathophysiological status of patients with T2D. Early detection of patients with type 2 diabetes at risk for diabetic kidney disease may be a key strategy for prevention and treatment of progressive renal damage. We aimed to identify a novel panel of biomarkers predicting eGFR decline in type 2 diabetes, using multiple biomarkers that represent different disease pathways speculated to contribute to the progression of diabetic kidney disease.

Methods

- A systematic data integration approach was used to select biomarkers representing different disease pathways
- Twenty-eight biomarkers were measured in 82 patients seen at an outpatient diabetes center in The Netherlands
- We compared the cross-validated explained variation (R^2) of two models to predict eGFR decline
  - The first model included only established risk markers
  - The second model tested a novel panel of biomarkers on top of the established risk markers
- Least absolute shrinkage and selection operator (LASSO) was used for model estimation
- The C-index was calculated to assess improvement in prediction of accelerated eGFR decline defined as <-3.0 mL/min/1.73m^2/year
- Median follow-up was 4.0 years

Results

Table1. Baseline characteristics in patients with type 2 diabetes and association with renal function decline (n=82)

Age (years)	63.5 ± 9.4
Male Gender (%)	44 (53.7)
Current smoker (%)	8 (9.6)
Body mass index (kg/m^2)	32.4 ± 6.3
Systolic blood pressure (mmHg)	135.2 ± 16.3
UACR (mg/mmol)	1.2 [0.5, 57.7]
eGFR (mL/min/1.73m^2)	77.9 ± 22.6
HDL Cholesterol (mmol/L)	1.3 ± 0.4
HbA_{1c} (%)	7.7 ± 1.3
ACEi or ARB medication (%)	27 (42.9)
Oral diabetic medication (%)	35 (55.6)

Results

Table 2. Optimal model of established risk markers and biomarkers, results from LASSO selection and bootstrap resampling (N=1000).

Variable	mean β	95% CI*	*p-value*	Selection probability†
Baseline UACR	-0.5	-0.8, -0.2	0.002	0.999
Baseline SBP	0.1	0.0, 0.1	0.012	0.994
MMP2 (fibrosis)	7.4	0.0, 0.1	0.018	0.993
TEK (angiogenesis)	-0.8	-1.4, -0.1	0.018	0.993
Baseline eGFR	-0.1	-0.1, 0.0	0.026	0.987
CTGF (fibrosis)	-5.9	-10.4, -0.9	0.026	0.987
MMP7 (fibrosis)	-0.5	-1.2, 0.0	0.078	0.966
Current vs. never smoker	-1.6	-3.9, 0.0	0.144	0.943
MMP8 (fibrosis)	0.5	0.0, 1.0	0.134	0.935
NPHS2 (fibrosis)	-1.5	-3.7, 0.0	0.206	0.908
MMP1 (fibrosis)	0.4	-0.1, 1.1	0.298	0.897
TNFR1 (inflammation)	-1.6	-4.0, 0.0	0.228	0.889
SOST (mineral metabolism)	1.0	0.0, 2.6	0.278	0.888
Use of oral diabetic medication	-1.1	-2.7, 0.0	0.274	0.884
MMP13 (fibrosis)	-0.4	-1.8, 1.0	0.798	0.820
Sex	0.8	-0.9, 2.8	0.592	0.785
CCL2 (inflammation)	0.5	-1.2, 2.7	0.854	0.781
YKL-40 (inflammation)	-0.4	-1.4, 0.0	0.518	0.771
NT-proCNP (endothelial function)	0.8	0.0, 2.5	0.568	0.742

*95% confidence interval, estimated from the 2.5th and 97.5th percentiles of the bootstrap distribution. †The relative frequency of the marker being included in the model across bootstrap resamples. *Biomarker (pathway) are listed in blue italics.*

Figure 1. LASSO selection of optimal model of established risk markers and biomarkers: cross validated mean squared error (Y-axis; red bullets; MSE) vs. amount of restriction (X-axis; log(Lambda)). Vertical bars refer to standard errors across the 82 cross-validations. The best cross-validated MSE was obtained after inclusion of 19 variables (step 31) (Variables from Table 2).

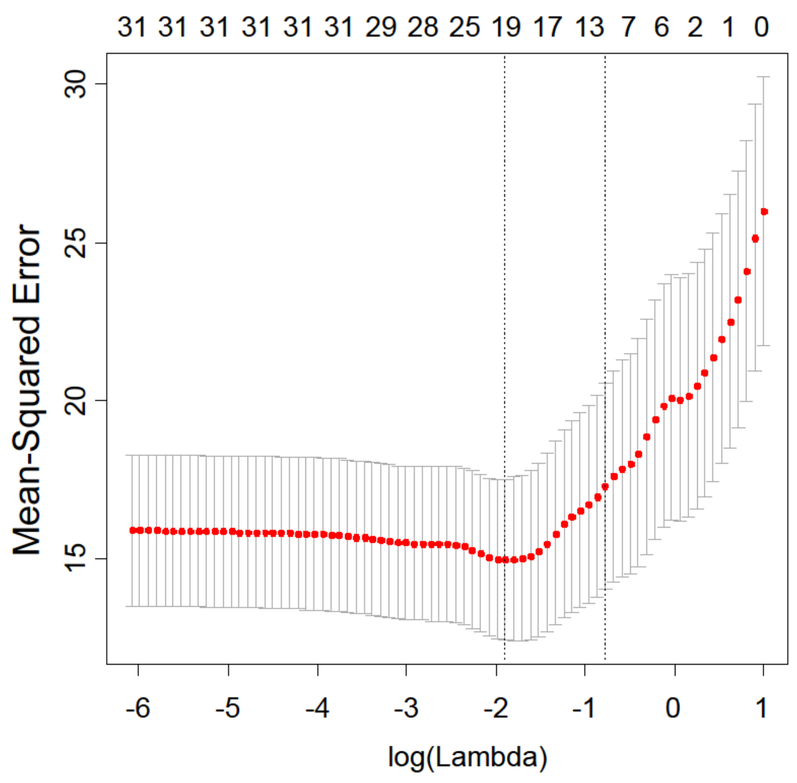
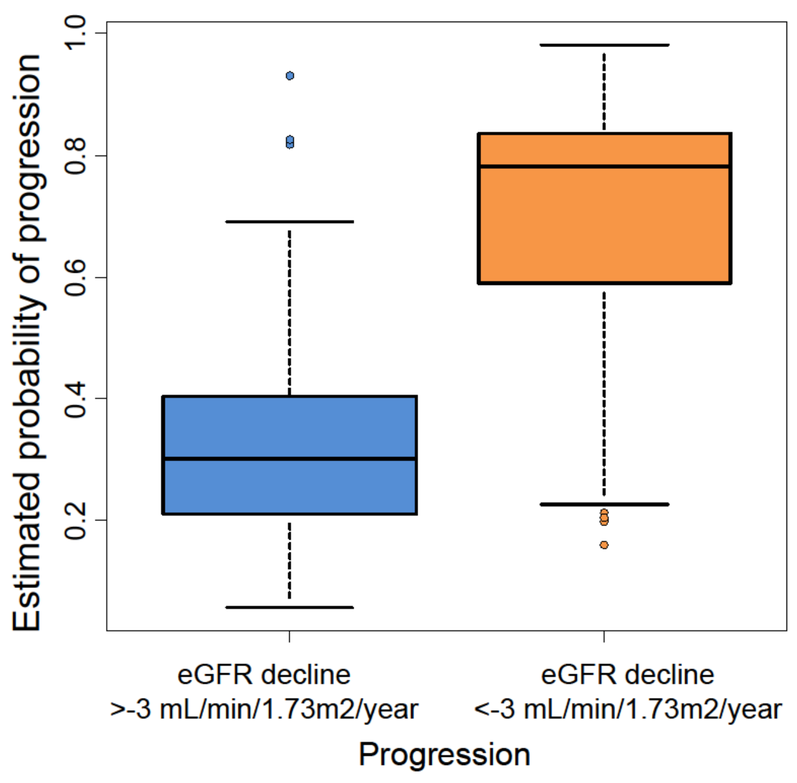


Table 3. Improvement in prediction of annual renal function decline and discrimination of accelerated renal function decline >3mL/min/1.73m^2/year between risk markers and biomarker panel.

	R^2	p-value	C-index	p-value
Established risk markers	0.377	Ref.	0.84	Ref.
+ Biomarker panel	0.546	0.018	0.90	0.008

Figure 2. Predicted probability of accelerated renal function decline (eGFR decline <-3 or >-3 mL/min/1.73m^2/year) in patients with type 2 diabetes for optimal model of established risk markers and biomarker panel.



Conclusion

A novel panel of biomarkers representing different pathways of renal disease progression including inflammation, fibrosis, angiogenesis, and endothelial function improved prediction of eGFR decline on top of established risk markers in type 2 diabetes. These results need to be confirmed in a large prospective cohort.

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