GRONINGEN KIDNEY CENTER

Creatinine, Cystatin C, Beta-2-Microglobulin and Beta-Trace Protein: which marker is best to assess changes in eGFR over time?

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Background

To assess kidney function creatinine based GFR estimation equations are generally used. New filtration markers, among which cystatin C (cys C), Beta-2-Microglobulin (B2M) and Beta-Trace protein (BTP) have been proposed for more accurate estimation of GFR. We investigated whether precision of eGFR slopes can be improved with the use of these novel filtration markers.

Methods

- Post-hoc analysis of the SUN-MACRO study, a cohort of 1179 patients with type 2 diabetes and nephropathy.
- Creatinine, cystatin C, B2M, and BTP were measured at baseline, and at 6, 12 and 18 months. eGFR was calculated with equations for creatinine, cys C, B2M and BTP.

Three methods were used to find the best eGFR equation:

- Sum of squares of all slopes were calculated for each eGFR equation (intra-individual variability).
- Linear mixed models were used to calculate eGFR slopes, and Levene's test was used for comparison of SDs (inter-individual slope variability).
- A multivariable linear regression analysis was performed to assess the strengths of associations of eGFR slopes with established kidney risk markers (R-squared).

Results

- Slopes were calculated for 968 patients in which at least 2 creatinine measurements were available. At baseline, patients had a mean age of 63.1 ± 9.1 years, 76% was male and 68% were Caucasian.
- Further results are shown in Tables 1 – 4.

Conclusion

This study shows that the eGFR slope has least intra individual variability when using a BTP based equation to estimate GFR. The inter individual variability was lowest for eGFR-B2M, leading to a sample size reduction of up to 17%. However, none of the novel filtration markers that can be used to calculate slopes of eGFR over time resulted in stronger associations of eGFR slope with established kidney risk factors when compared to creatinine based eGFR. This questions whether these novel markers provide additional value beyond creatinine.

Table 1: Intra-individual variability of eGFR slopes

No of measurements (N)	$eGFR_{creat}$	$eGFR_{cysc}$	$eGFR_{b2m}$	$eGFR_{btp}$
Overall	79 ± 172	107 ± 217*	62 ± 102	**53 ± 119***
3 (313)	53	63	37	**29**
4 (271)	94	127	76	**52**
5 (142)	108	167	**89**	107

Table 2: Inter-individual variability for baseline eGFR and eGFR slopes

	$eGFR_{creat}$	$eGFR_{cysc}$	$eGFR_{b2m}$	$eGFR_{btp}$
Baseline eGFR (ml/min/1.73m²)	30.1 ± 9.4	29.2 ± 11.4	30.4 ± 9.1	31.9 ± 8.8
eGFR slope ± SD (ml/min/1.73m² per year)	-5.4 ± 7.0	-6.1 ± 7.9*	**-4.9 ± 5.9***	4.2 ± 6.3*

Table 3: Sample size calculation for 20% and 25% slope reduction (β 0.8, α 0.05)

	$eGFR_{creat}$	$eGFR_{cysc}$	$eGFR_{b2m}$	$eGFR_{btp}$
20% slope reduction	636	681 +7%	**547 -14%**	963 +51%
25% slope reduction	456	436 -4%	**380 -17%**	624 +37%

Table 4: Associations of eGFR slopes with renal risk factors

Multivariable		$eGFR_{creat}$	$eGFR_{cysc}$	$eGFR_{b2m}$	$eGFR_{btp}$
Adjusted R^2		**0.066**	**0.084**	0.040	0.033
Age	Stand β	0.127	0.130	0.068	-0.006
	p-value	**0.002**	**0.001**	0.1	0.9
Female	β	0.227	0.833	0.340	0.632
	p-value	**0.04**	**<0.001**	**<0.001**	**<0.001**
Smoking	β	-0.079	0.206	-0.012	0.010
	p-value	0.6	0.2	0.9	1.0
BMI	Stand β	0.052	0.078	0.038	-0.013
	p-value	0.2	**0.05**	0.4	0.8
SBP	Stand β	0.015	0.037	0.037	0.078
	p-value	0.7	0.3	0.3	**0.05**
HbA1c	Stand β	-0.008	-0.03	-0.019	-0.052
	p-value	0.8	0.5	0.6	0.2
Total	Stand β	-0.033	-0.083	-0.047	-0.107
Cholesterol	p-value	0.4	**0.03**	0.2	**0.007**
Ln(UACR)	Stand β	-0.120	0.004	-0.078	-0.054
	p-value	**<0.001**	0.9	0.1	0.2

**=p<0.05 vs $eGFR_{creat}$*

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