A NMR-BASED BIOMARKER CONSTELLATION FOR GFR PREDICTION ENABLES METABOLIC PHENOTYPING

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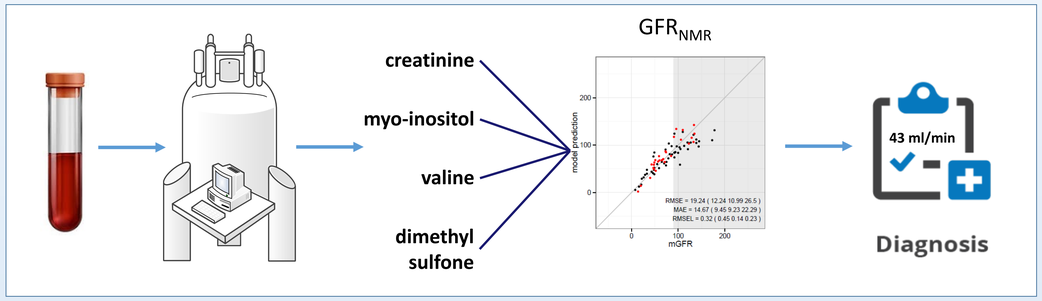
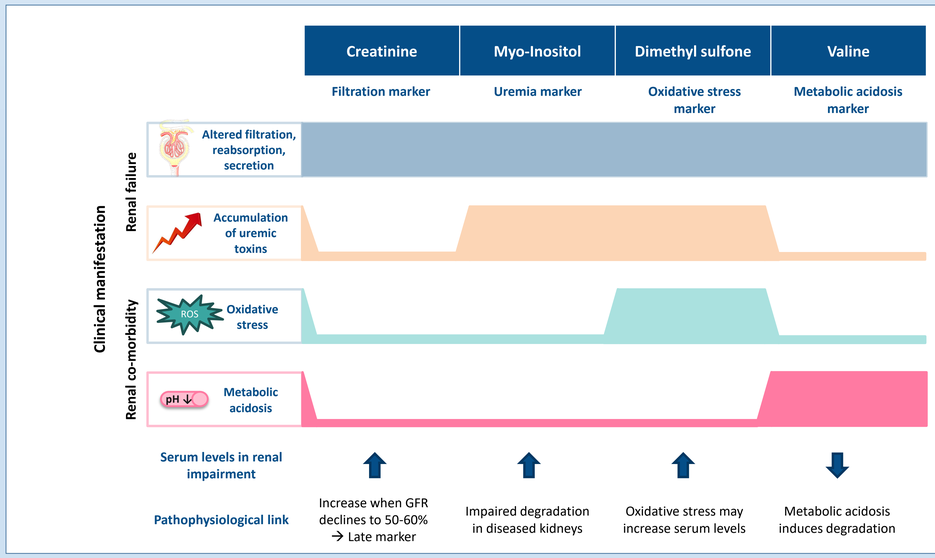
BACKGROUND

Assessment of kidney function by radioactive clearance measurements (mGFR) or estimated GFR by moderately-performing equations (eGFR) is integral to management of kidney disease. Recently, we developed a novel method for accurate prediction of GFR, based on a serum biomarker constellation of creatinine, myo-inositol, valine and dimethyl sulfone analyzed by nuclear magnetic resonance (NMR) spectroscopy. This metabolite constellation was tested and validated in three separate cohorts in a multi-center study.



METHODS

In order to characterize the role of these biomarkers in renal dysfunction and pathogenesis of CKD and to test their value for metabolic phenotyping, biomarker profiling was applied to sets of three age-, and mGFR-matched male patients with CKD stage II during end-stage liver disease. In order to compare the obtained profiles, measured biomarker concentrations were transformed into z-scores. This allows a direct comparison of the observed fold-changes from one marker to the other. The obtained z-scores were plotted in a chart with one axis for creatinine (as a marker of filtration), a second for dimethyl sulfone (as a marker of oxidative stress), a third axis for myo-inositol (as a maker of uremia), and a fourth axis for valine (as a marker of metabolic acidosis).

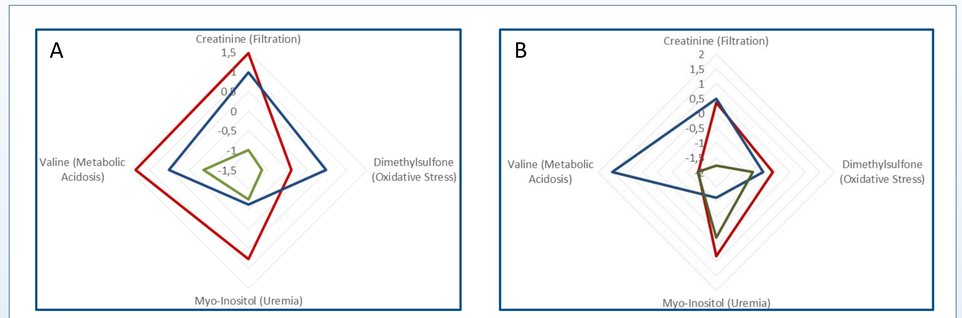


RESULTS

Within two age- and mGFR-matched sets, the metabolic profiles of these clinically similar patients differed significantly concerning single markers reflecting filtration, uremic toxins, oxidative stress, and acidosis.

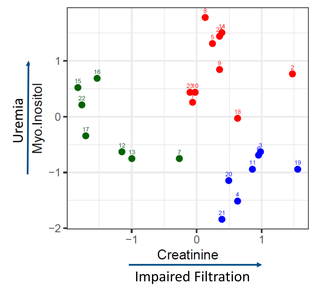
Patients depicted in red and blue showed above average z-scores for creatinine and valine, while the patient depicted in green had below average z-scores for creatinine, dimethyl sulfone, myo-inositol, and valine (panel A). This observation would be compatible with the conclusion that the patient depicted in green had only minimal levels of oxidative stress, whereas patients in red and blue showed average or increased levels.

The three matched patients with measured GFR of 78 ml/min/1.73m² had very similar and average levels of oxidative stress (panel B). The patient depicted in blue showed a higher level of valine reflecting metabolic acidosis and a lower level of myo-inositol reflecting uremia if compared to the matched patients depicted in green and red.



Patient GW11465(76)		Patient BJP2953(50)		Patient CD24554(54)	
Sex	male	Sex	male	Sex	male
Age	52.9 yrs	Age	63.1 yrs	Age	63.5 yrs
BMI	27.2 kg/m²	BMI	26.5 kg/m²	BMIt	26.0 kg/m²
mGFR	62 ml/min/1.73m²	mGFR	62 ml/min/1.73m²	mGFR	63 ml/min/1.73m²

Patient TGB22257(106)		Patient DY13347(67)		Patient PLP1255(100)	
Sex	male	Sex	male	Sex	male
Age	60.6 yrs	Age	68.7 yrs	Age	62.0 yrs
BMI	20.7 kg/m²	BMI	25.5 kg/m²	BMIt	24.6 kg/m²
mGFR	79 ml/min/1.73m²	mGFR	78 ml/min/1.73m²	mGFR	78 ml/min/1.73m²



Three clusters:

(1) Above average GFR with low levels of uremic toxicity (blue)
(2) Above average GFR with high levels of uremic toxicity (red)
(3) Below average GFR with average level of uremic toxicity (green)

Myo-inositol in liver failure

- Principal cause of mortality in patients with acute liver failure is brain herniation due to hepatic encephalopathy (HE)
- Brain herniations results from increased brain water
- Myo-inositol as a uremic toxin is a brain organic osmolyte and associated with severity of hepatic encephalopathy

CONCLUSIONS

These observations suggest that the set of renal biomarkers enables molecular phenotyping of clinically highly selected age-, sex-, and mGFR-matched patients of homogenous clinical etiology providing further insights into their individual renal comorbidities based upon complex design thinking and a single diagnostic method using one serum sample.

CONTACT DETAILS

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