Application of MRI to DKD: evidence to date

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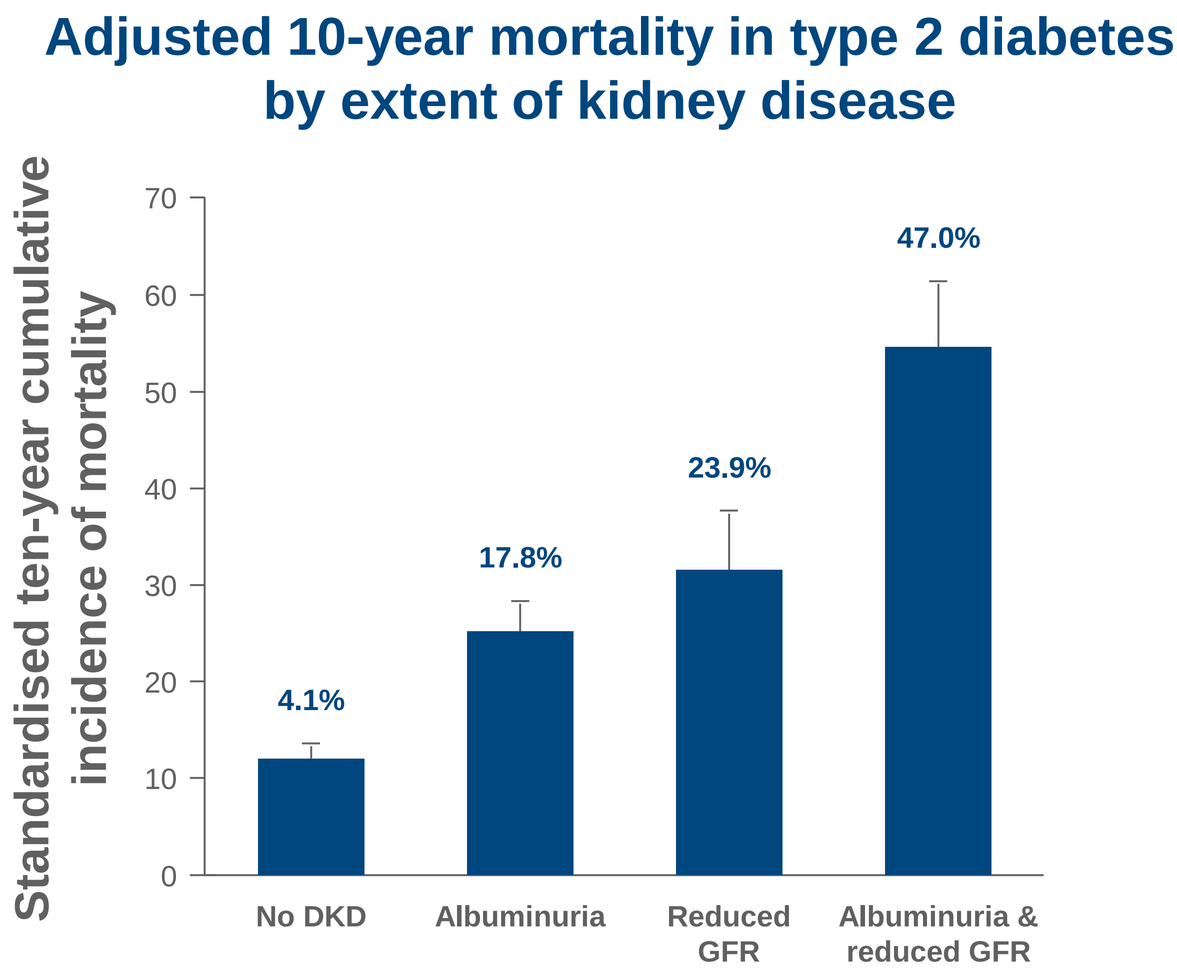
Outline

- Rationale for multi-parametric renal MRI in DKD
- What can renal MRI do right now in DKD?
  - Tissue characterisation (oxygenation, perfusion, fibrosis)
  - Disease progression
  - Disease mechanism
  - Treatment response
- Pending clinical renal MRI studies in DKD

DKD is the main cause of death in those with type 2 diabetes

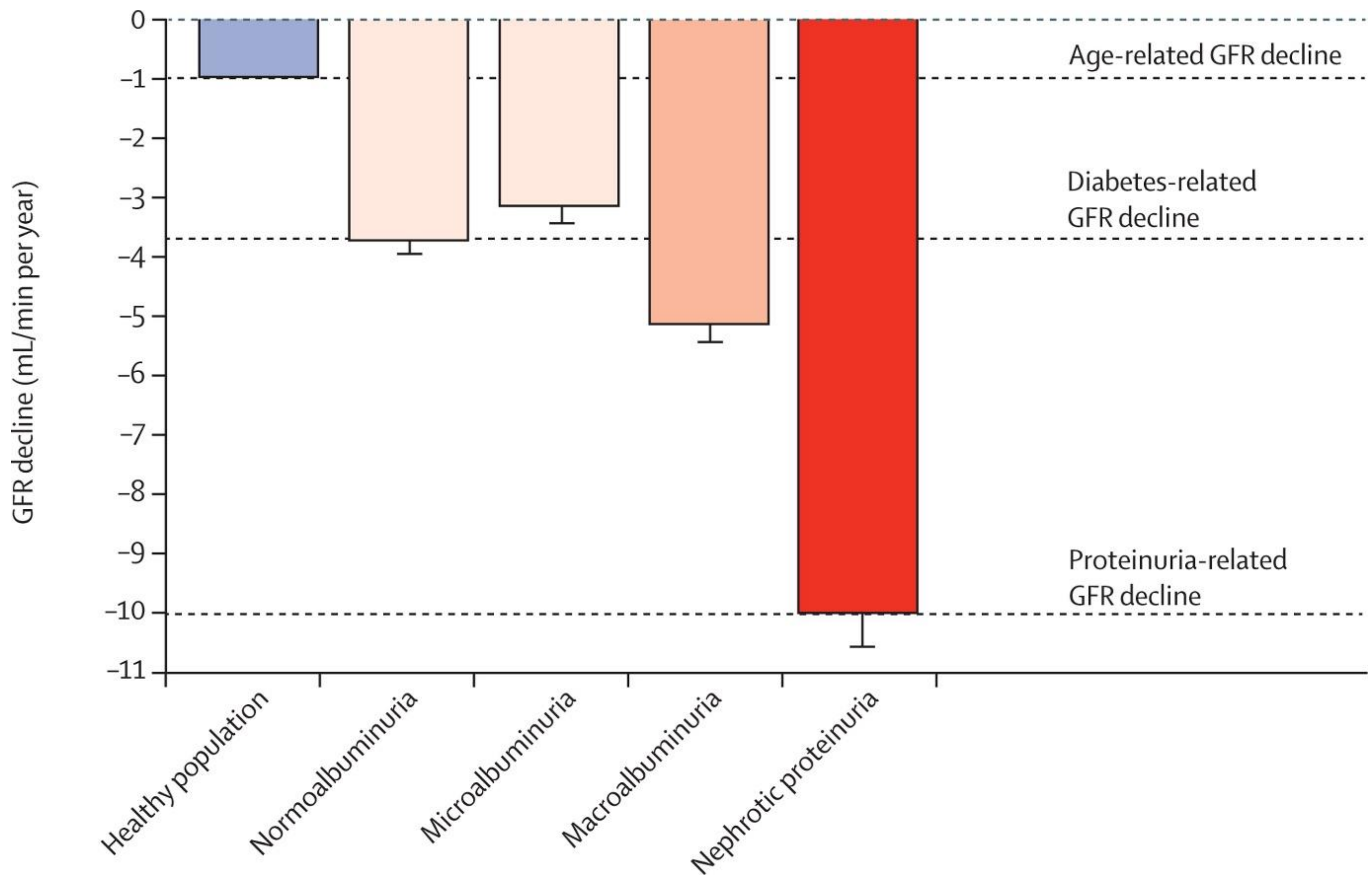


Afkarian et al. *J Am Soc Nephrol* 24: 302–308, 2013

Current biomarkers of DKD explain only 50% of GFR decline

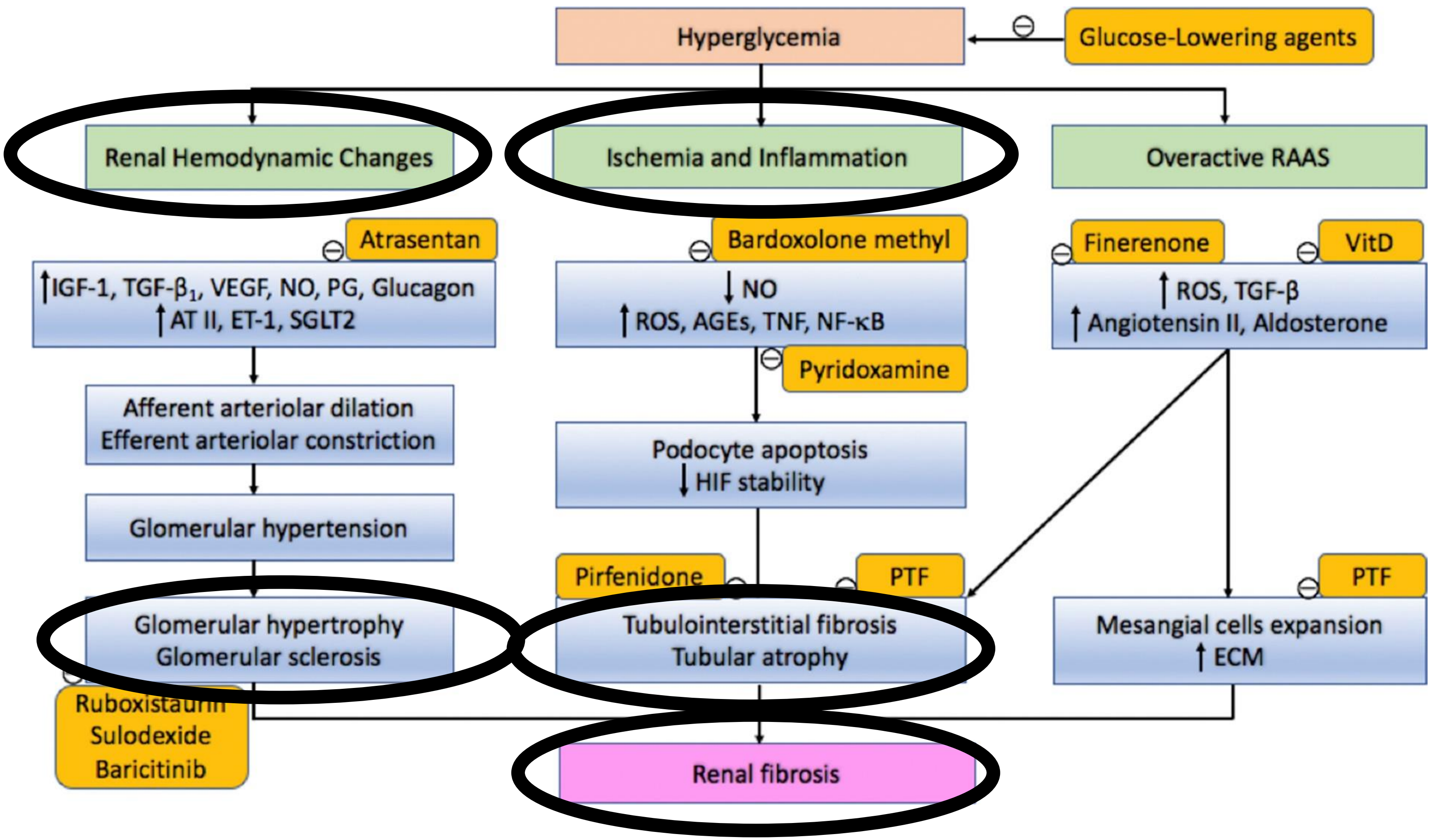
Non-proteinuric pathways in loss of renal function in patients with type 2 diabetes

Esteban Porrini, Piero Ruggenenti, Carl Erik Mogensen, Drazenka Pongrac Barlovic, Manuel Praga, Josep M Cruzado, Radovan Hojs, Manuela Abbate, Aiko P J de Vries, for the ERA-EDTA diabesity working group.

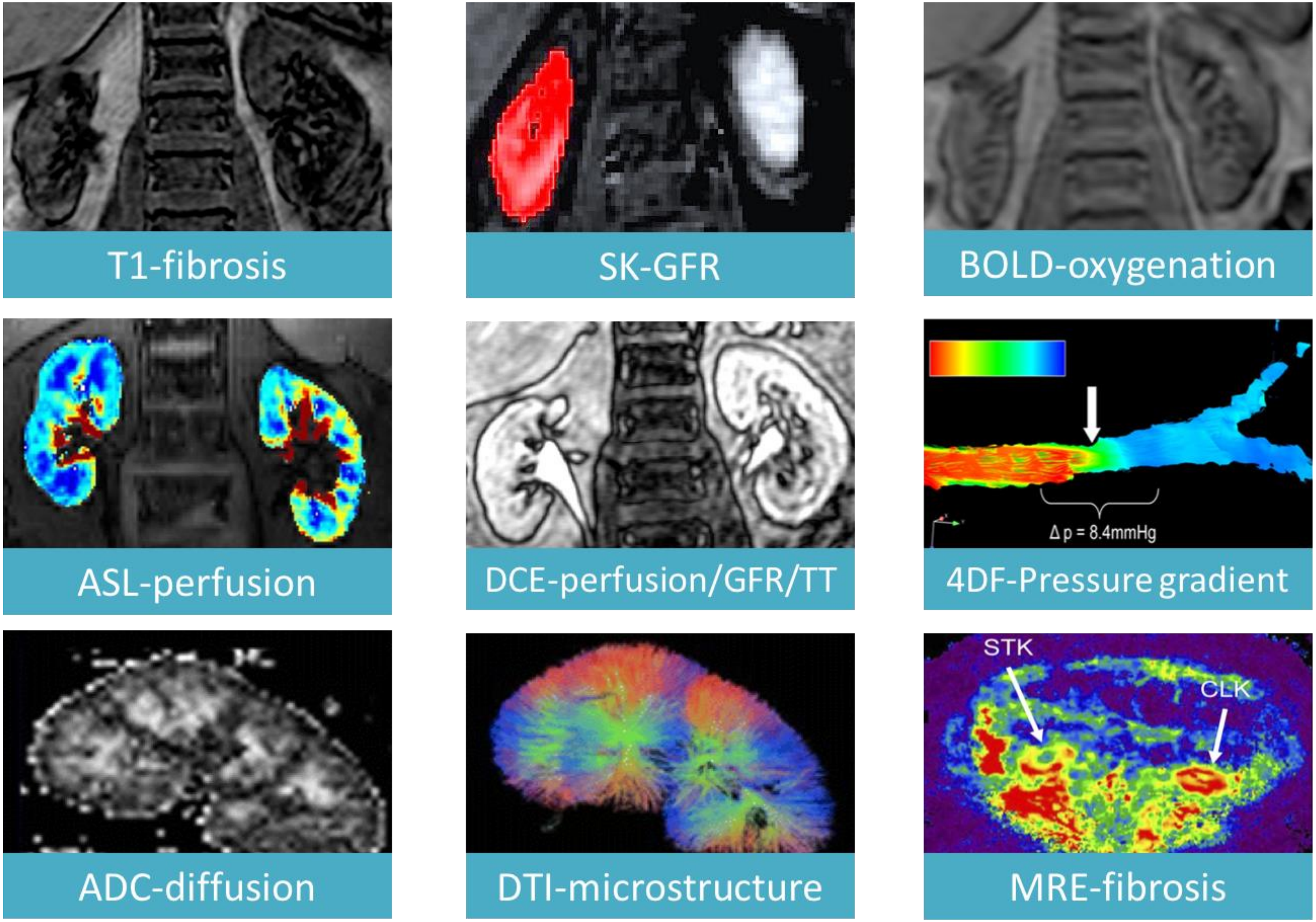


The Lancet Diabetes & Endocrinology 2015 3, 382-391

Potential of renal functional MRI to characterise pathology of DKD and provide mechanistic insights to novel therapy



Multi-parametric imaging



Rationale for renal MRI as biomarker in DKD

- FDA/EMEA approved renal outcomes in RCTs
  - 50% ↓eGFR, 2x↑Creatinine, Dialysis
- Phase 2a commercial drug trial needs n>800, >4 years and costs £>100M
- Albuminuria can be unreliable surrogate ~50% of ΔeGFR
- **MRI may reduce trial length and costs**
- **MRI provides drug mechanism insights prior to larger trials**
- **MRI may detect changes earlier than GFR decline** (RBF and TKV in PKD for Tolvaptan)

Rationale for MRI as in-vivo microscopy

- 1 million glomeruli in a kidney
- 5-20 in a typical biopsy (0.002% sample)
- 30% fibrosis in biopsy 95%CI(5-70%) whole kidney
- Biopsy safe, but rare complications
  - 1% major bleed
  - 0.1% surgery/death
- MRI assesses whole kidney; may complement or replace biopsy

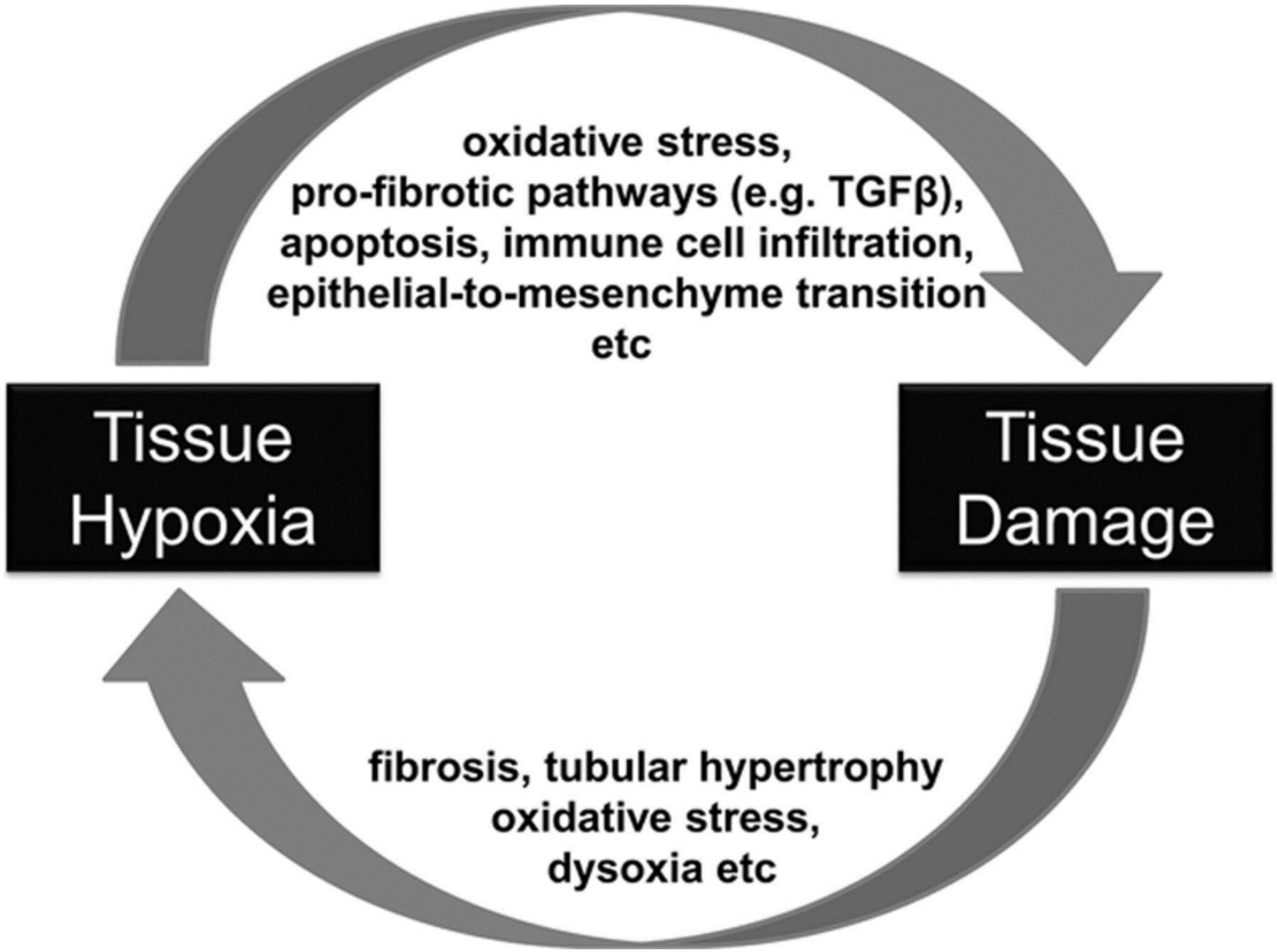
Corwin Am J Neph 1988

Multiparametric MRI as a biomarker for DKD

MR technique	**Biomarker**
Arterial Spin-Labelling (ASL)	Regional Tissue perfusion
BOLD	Oxygenation
DCE-MRI	Single kidney GFR, tissue blood flow
	Tubular flow, Filtration fraction
	Tubular transit time, Tubular volume fraction
Diffusion weighted imaging (DWI)	Tissue oedema and fibrosis
Diffusion-tensor imaging (DTI)	Tissue structure
Emerging molecular techniques (Na or P spectroscopy, CEST)	Sodium, phosphate, amino-acids
Magnetization transfer	Tissue structure
MR elastography	Tissue fibrosis
Phase contrast	Total blood flow and velocity
T_1 mapping	Tissue volume, oedema and fibrosis
T_2 mapping	Tissue volume, oedema and fibrosis
Volume	Total Kidney Volume (TKV)
	Cortical volume
	Total cyst volume in ADPKD

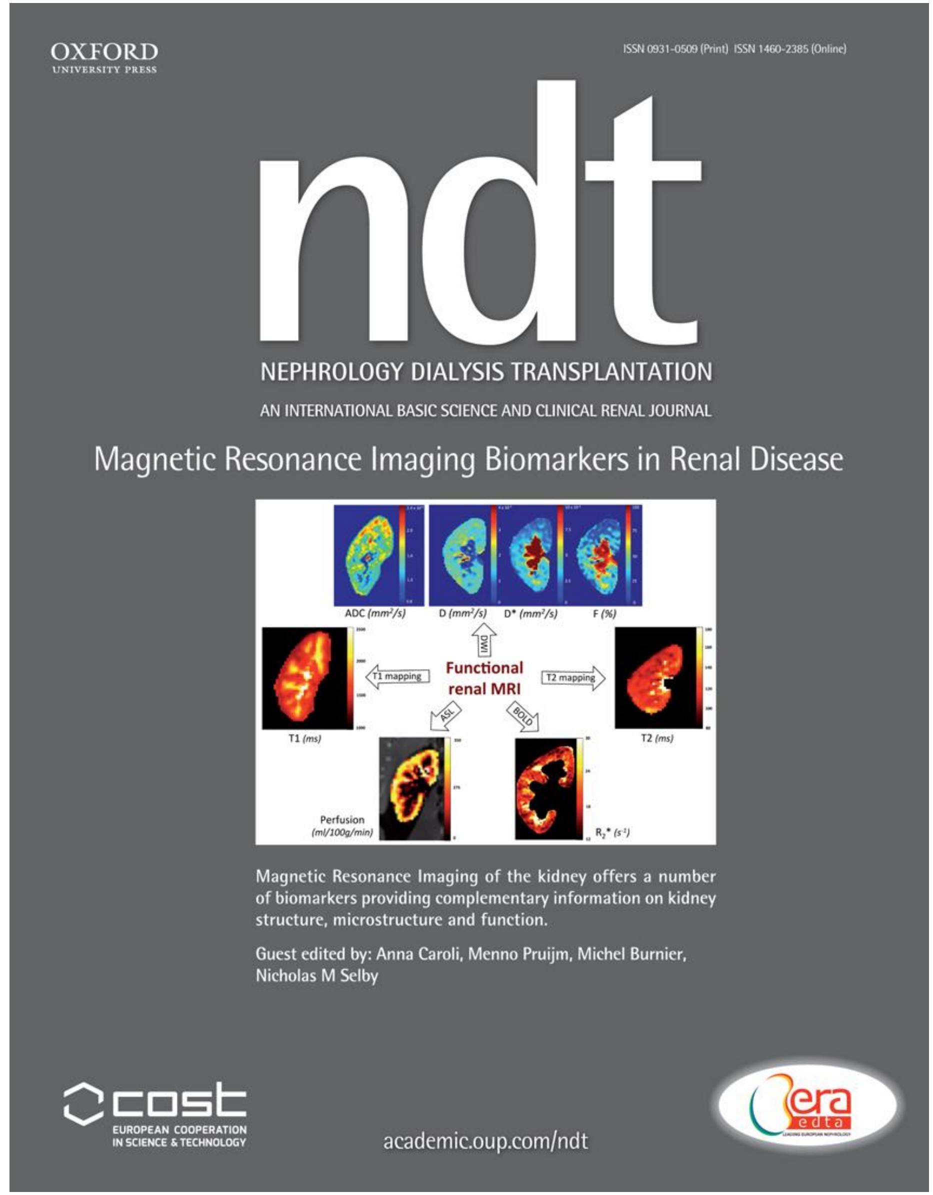
Oxygenation by Blood-Oxygen Level Dependent imaging (BOLD) T2*/R2* mapping

The proposed vicious cycle of hypoxia and renal tissue damage that drives the progression of DKD



Roger G. Evans, and Paul M. O'Connor Hypertension. 2013;62:827-828

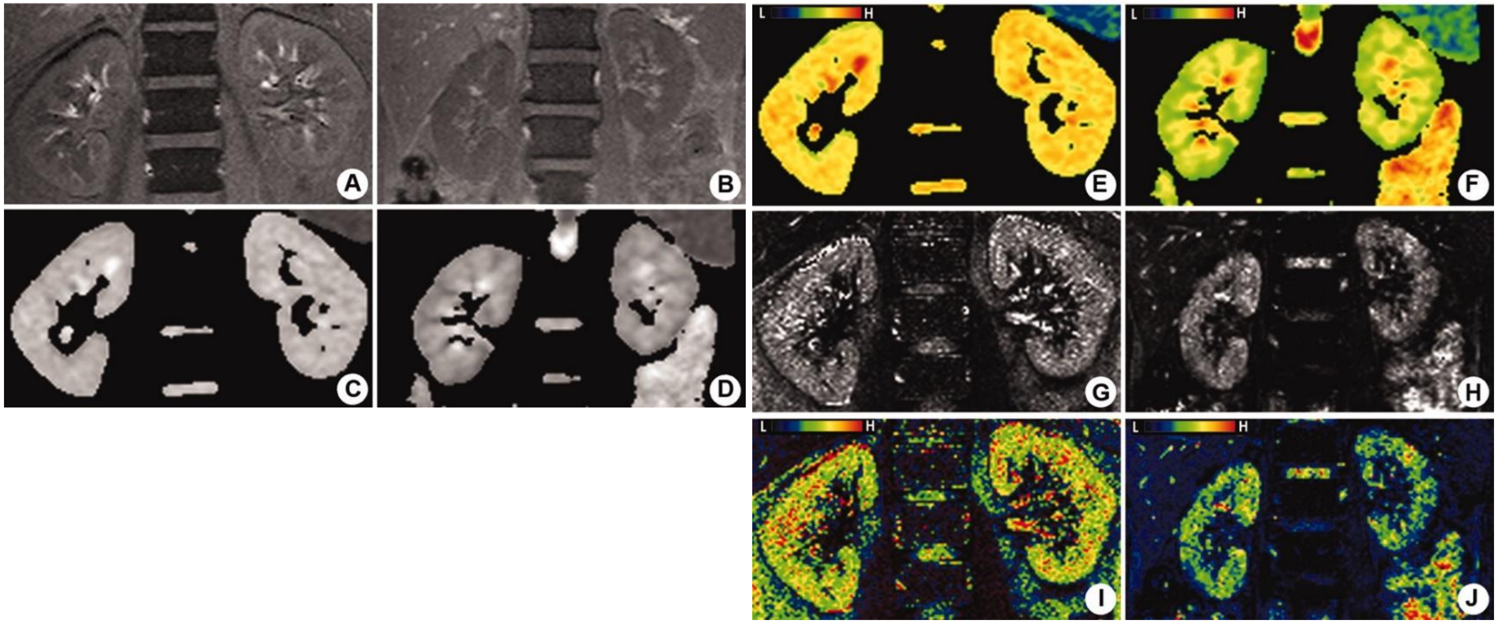
- Open access
- State of the art reviews on renal fMRI for CKD



NDT Volume 33, Issue suppl_2, September 2018,

BOLD (Blood-Oxygen Level Dependent) Imaging

- Deoxygenated Hb = weakly magnetic
- More O_2> Less deoxyHb > Less dephasing > Longer T2* > Shorter R2*(=1/T2*)
- Validated against implanted O_2-sensing electrodes



Inoue et al. JASN 2011;22:1429

Overview of prior cross-sectional studies that have used BOLD-MRI to assess renal tissue oxygenation in DKD compared with controls generally show more hypoxia but inconsistent changes and ROI matters

Author	Year	N	Design	Field strength (Tesla)	Analysis method	R2* cortex	R2* medulla
Inoue	2011	119	DKD-control	1.5	ROI	No difference	Not available
Wang	2011	27	DKD-control	1.5	ROI	No difference	Lower in DKD
Yin	2012	115	DKD-control	3	ROI	Higher in DKD	
Thelwall	2011	17	DKD-control	3	ROI	No difference	
Prasad	2015	30	DKD-control	3	ROI	Higher in DKD	
Feng	2019	30	DKD	3	ROI	No difference	Higher in DKD with albuminuria

Diabetes Res Clin Pract. 2019 Apr;150:138-143. doi: 10.1016/j.diabres.2019.03.009. Epub 2019 Mar 11.

Acute hyperglycemia increases renal tissue oxygenation as measured by BOLD-MRI in healthy overweight volunteers.

Vakilzadeh N[1], Zanchi A[1], Milani B[2], Ledoux JB[3], Braconnier P[1], Burnier M[1], Pruijm M[4].

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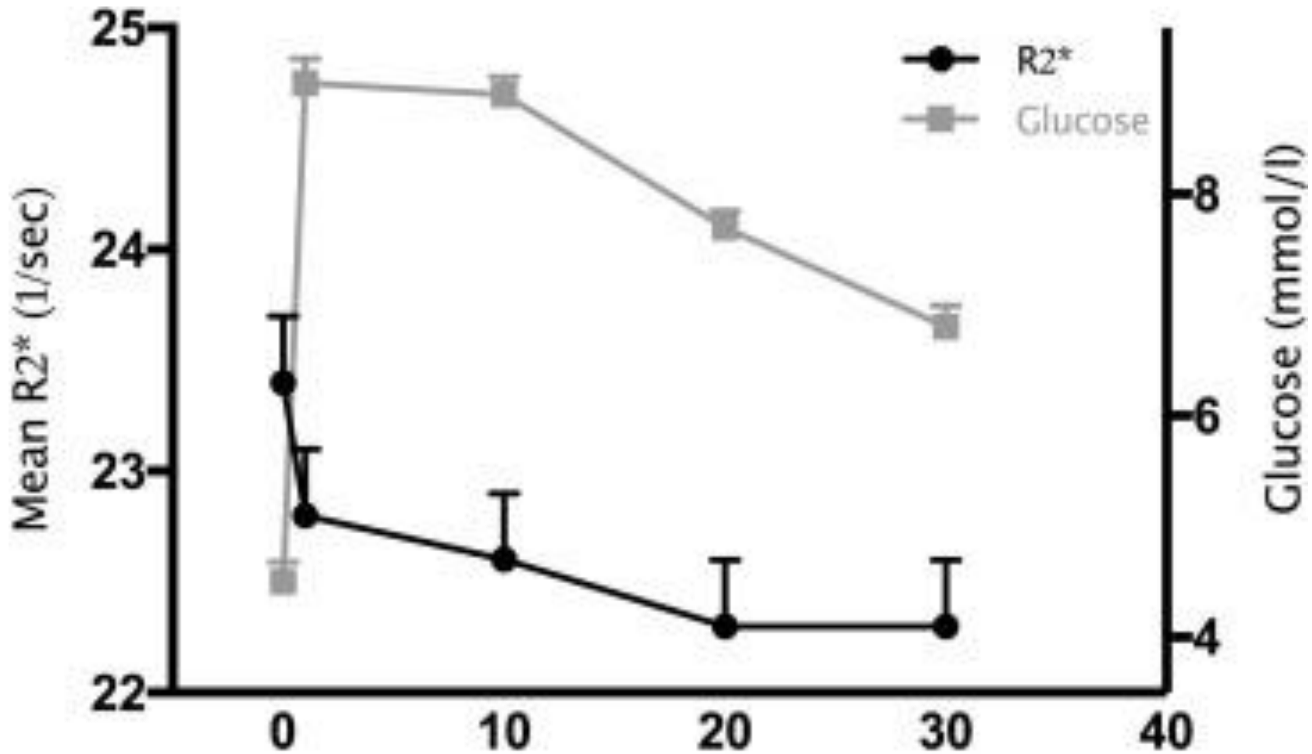
4 Service of Nephrology and Hypertension, University Hospital Lausanne (CHUV), Switzerland. Electronic address: menno.pruijm@chuv.ch.

Changes in R2* and blood glucose after glucose injection in healthy overweight volunteers



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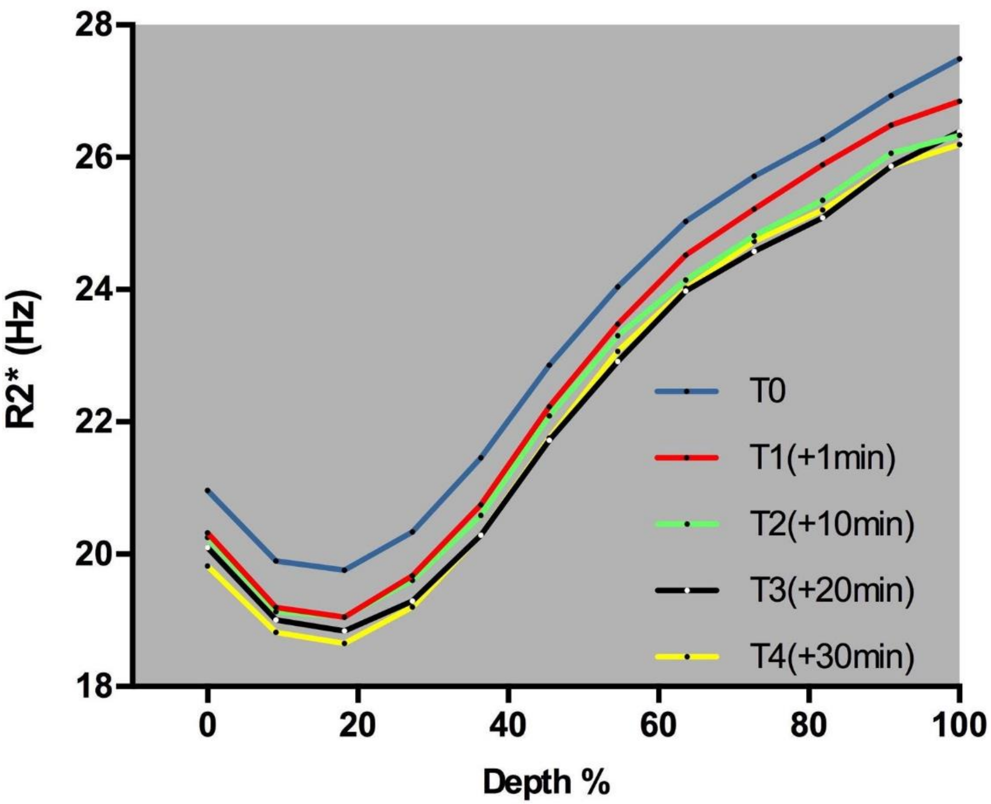
3 CIBM & Department of Radiology, CHUV, Lausanne, Switzerland.
4 Service of Nephrology and Hypertension, University Hospital Lausanne (CHUV), Switzerland. Electronic address: menno.pruijm@chuv.ch.

Change in R2* profile across the kidney after glucose injection in 19 healthy obese volunteers (of which 5 have IGT or pre-diabetes)

These data confirm for the first time in humans that acute hyperglycemia decreases the R2* signal in humans, suggesting an acute increase in renal tissue oxygenation in contrast to animal data where hyperglycaemia causes hypoxia.

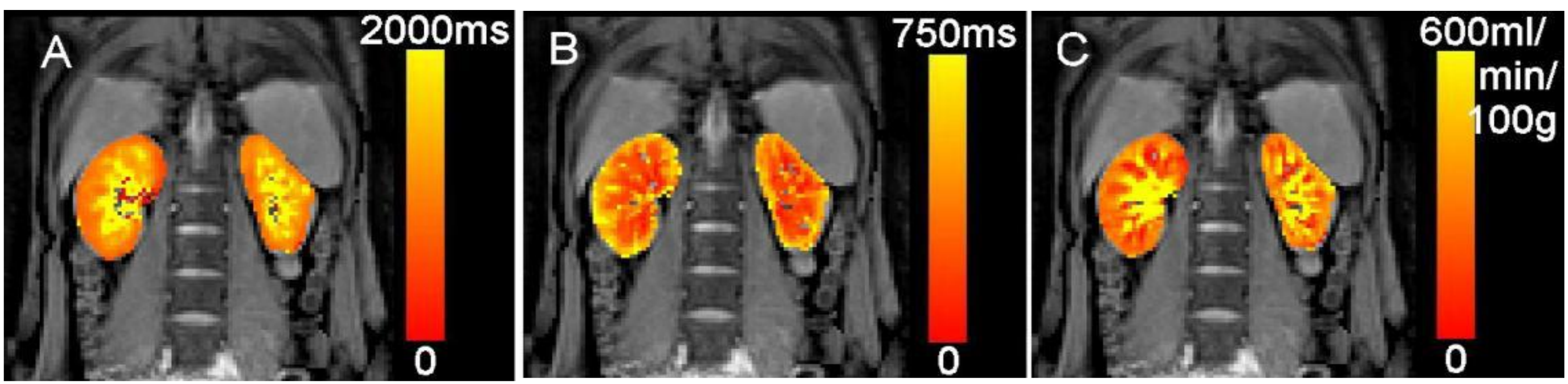
Interpretation is complex given the confound nature of R2* but concurrent measurement of glucose and renal perfusion (ASL) will be relevant



Non-contrast perfusion with arterial spin-labelling (ASL)

Non-contrast perfusion with arterial spin-labelling (ASL)

Control **Labelled** **Perfusion Weighted Image**



Odudu et al. NDT 2018 (image by Charlotte Buchanan)

Nephrol Dial Transplant (2018) 33: ii15–ii21
doi: 10.1093/ndt/gfy180

Arterial spin labelling MRI to measure renal perfusion: a systematic review and statement paper

Aghogho Odudu[1], Fabio Nery[2], Anita A. Harteveld[3], Roger G. Evans[4], Douglas Pendse[5], Charlotte E. Buchanan[6], Susan T. Francis[6] and María A. Fernández-Seara[7]

ASL perfusion correlates with eGFR in CKD but few specific studies in DKD

Reference	Setting	eGFR method	r-value
Breidthardt-2015	CKD	MDRD	0.52
Gillis-2016	CKD	CKD-EPI	0.73
Li-2017	CKD	CKD-EPI	0.67
Mora-Gutierrez-2017	CKD	MDRD	0.62
Artz-2011	Healthy volunteer/Transplant	MDRD	0.85/0.62
Heusch-2014	Transplant	MDRD	0.59
Hueper-2015	Transplant	MDRD	0.64

J Magn Reson Imaging. 2017 Dec;46(6):1810-1817. doi: 10.1002/jmri.25717. Epub 2017 Apr 6.

Arterial spin labeling MRI is able to detect early hemodynamic changes in diabetic nephropathy.

Mora-Gutiérrez JM[1], Garcia-Fernandez N[1], Slon Roblero MF[2], Páramo JA[3], Escalada FJ[4], Wang DJ[5], Benito A[6], Fernández-Seara MA[6,7].

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5 Laboratory of Functional MRI Technology (LOFT) Stevens Neuroimaging and Informatics Institute University of Southern California, Los Angeles, California, USA.
6 Radiology, Clínica Universidad de Navarra, Spain.
7 Adjunct Associate Professor of Radiology, University of Pennsylvania, Philadelphia, Pennsylvania, USA.

Abstract

PURPOSE: To investigate whether arterial spin labeling (ASL) MRI could detect renal hemodynamic impairment in diabetes mellitus (DM) along different stages of chronic kidney disease (CKD).

MATERIALS AND METHODS: Three Tesla (3T) ASL-MRI was performed to evaluate renal blood flow (RBF) in 91 subjects (46 healthy volunteers and 45 type 2 diabetic patients). Patients were classified according to their estimated glomerular filtration rate (eGFR) as group I (eGFR > 60 mL/min/1.73 m^2), group II (60 ≥ eGFR>30 mL/min/1.73 m^2), or group III (eGFR ≤ 30 mL/min/1.73 m^2), to determine differences depending on renal function. Studies were performed at 3T using a 12-channel flexible body array combined with the spine array coil as receiver.

RESULTS: A 28% reduction in cortical RBF was seen in diabetics in comparison with healthy controls (185.79 [54.60] versus 258.83 [37.96] mL/min/100 g, $P < 3 \times 10^{-6}$). Differences were also seen between controls and diabetic patients despite normal eGFR and absence of overt albuminuria (RBF [mL/min/100 g]: controls=258.83 [37.96], group I=208.89 [58.83], P = 0.0018; eGFR [mL/min/1.73 m^2]: controls = 95.50 [12.60], group I = 82.00 [20.76], P > 0.05; albumin-creatinine ratio [mg/g]: controls = 3.50 [4.45], group I = 17.50 [21.20], P > 0.05). A marked decrease in RBF was noted a long with progression of diabetic nephropathy (DN) through the five stages of CKD ($\chi^2 = 43.58$; $P = 1.85 \times 10^{-9}$). Strong correlation ($r = 0.62$; $P = 4 \times 10^{-10}$) was obtained between RBF and GFR estimated by cystatin C.

CONCLUSION: ASL-MRI is able to quantify early renal perfusion impairment in DM, as well as changes according to different CKD stages of DN. In addition, we demonstrated a correlation of RBF quantified by ASL and GFR estimated by cystatin C.

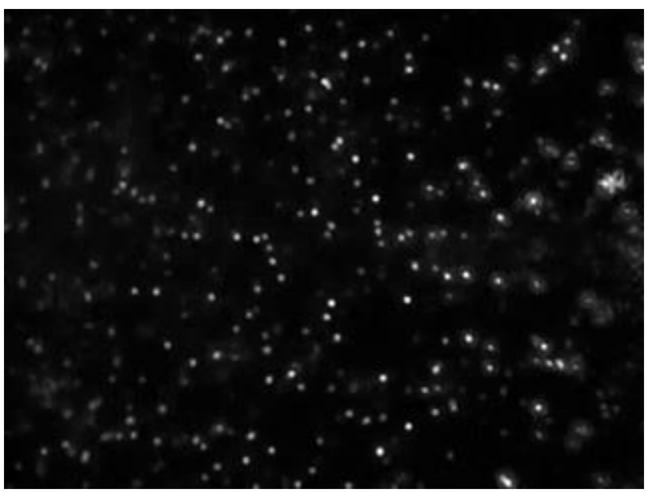
LEVEL OF EVIDENCE: 3 Technical Efficacy: Stage 2 J. Magn. Reson. Imaging 2017;46:1810-1817.

Diffusion Weighted imaging (DWI)
Diffusion Tensor Imaging (DTI)

Principles of Diffusion imaging

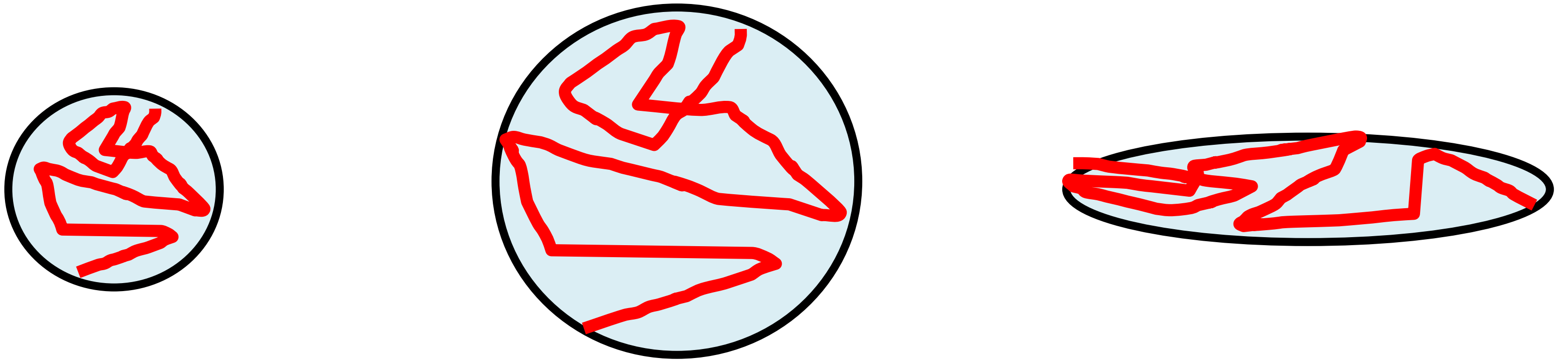
Robert Brown (1827): English botanist who observed pollen grain in water under a microscope and described they a ‘constant state of agitation’.

Brownian Motion



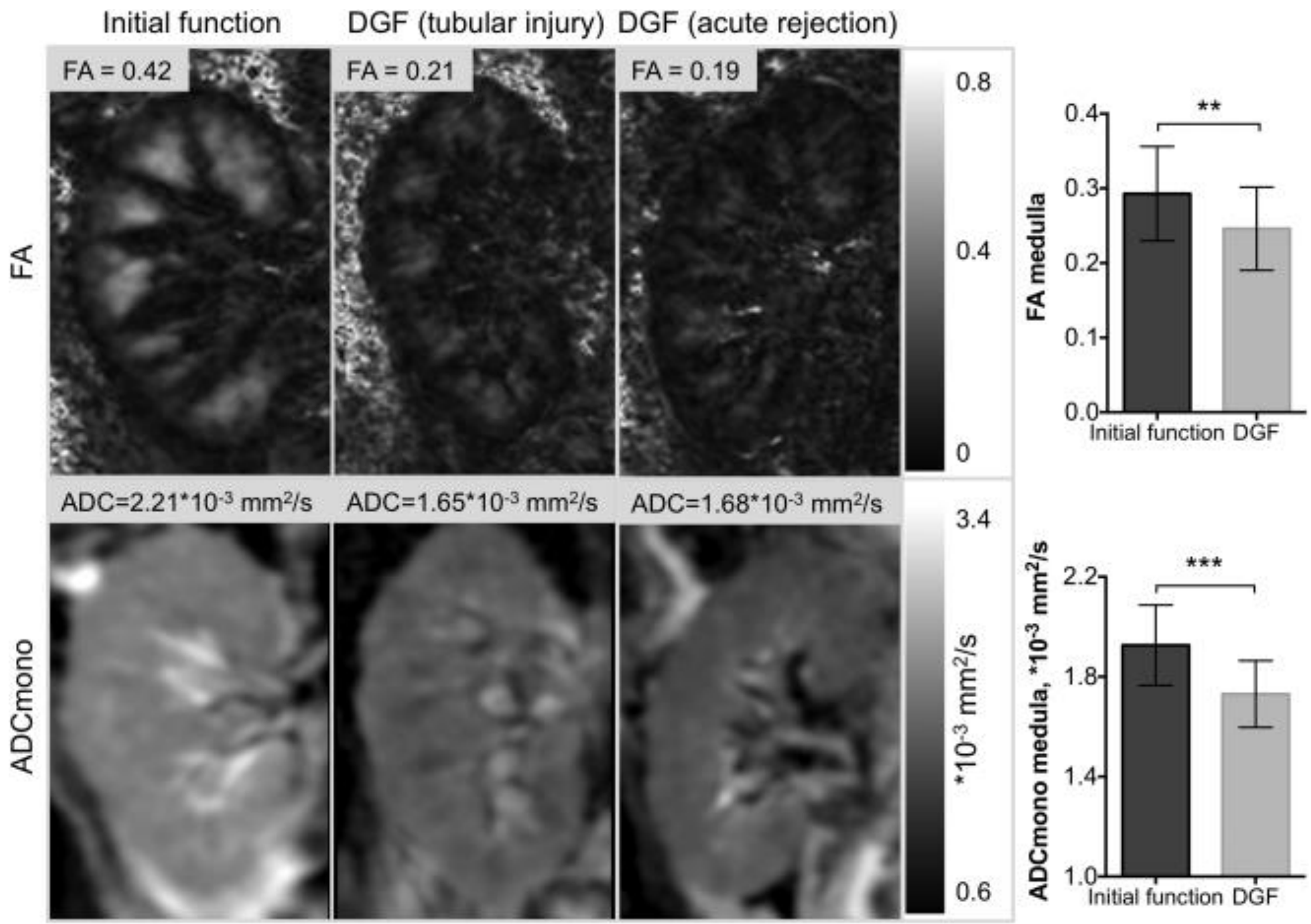
Principles of Diffusion imaging

- Cell membranes restrict water diffusion
- Mean Diffusivity measures degree of restriction
- Anisotropy measures directional dependency of restriction
- Tissue fibrosis, oedema and ischemia alter diffusion



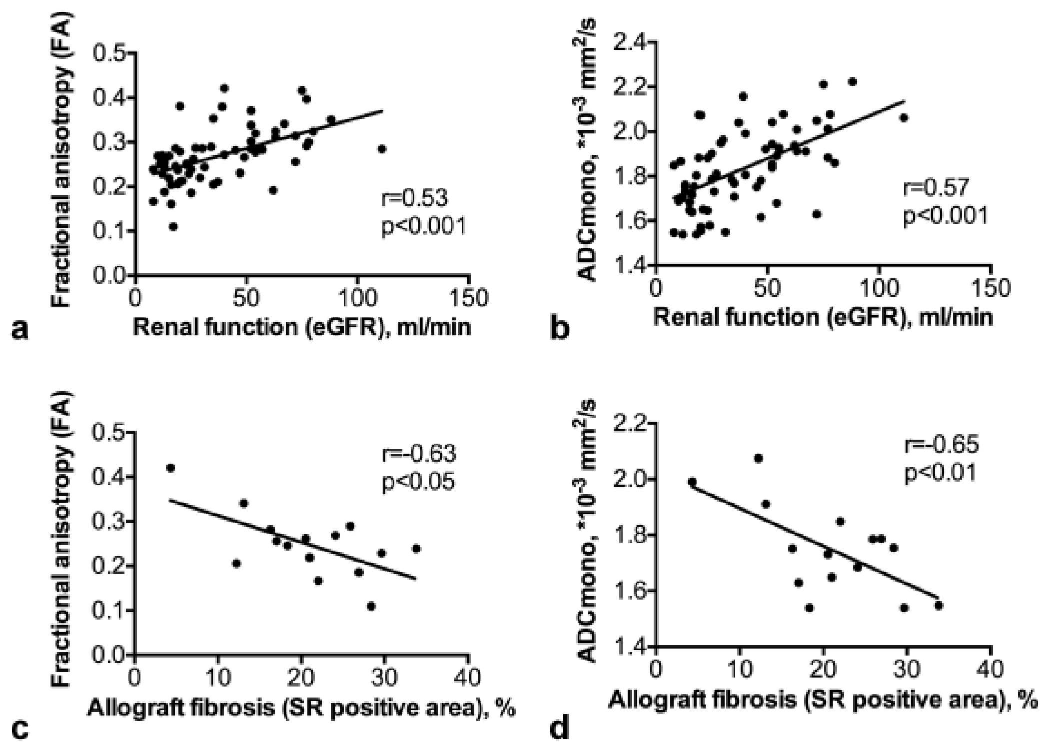
Mean Diffusivity **Fractional Anisotropy**

Diffusion-Weighted imaging and diffusion tensor imaging detect delayed graft function and correlate with allograft fibrosis in 26 patients early after kidney transplantation



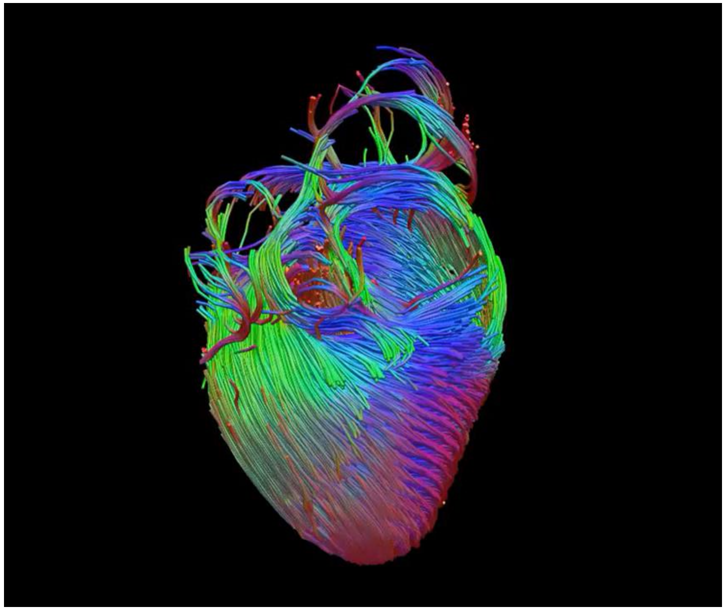
Hueper et al. Journal of Magnetic Resonance Imaging 2016

Diffusion-Weighted imaging and diffusion tensor imaging detect delayed graft function and correlate with allograft fibrosis in 26 patients early after kidney transplantation



Hueper et al. Journal of Magnetic Resonance Imaging 2016

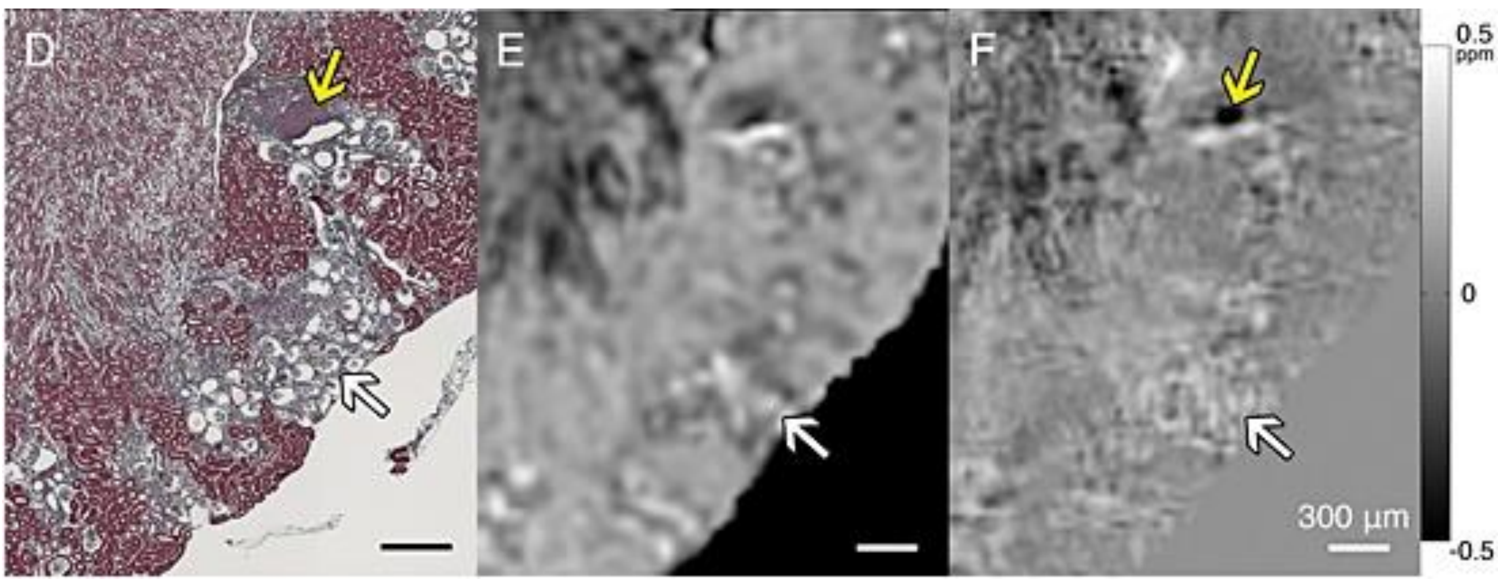
Tractography by Diffusion Tensor Imaging



Images by Luke Xie from Duke Center for In Vivo Microscopy

In-vivo Microscopy: Quantitative susceptibility mapping of kidney inflammation and fibrosis in murine model at 9.4T

Histology T2*W QSM



Xie et al NMR in Biomedicine 2013

The future: multi-parametric renal MRI

Adv Ther (2018) 35:875–885
https://doi.org/10.1007/s12325-018-0708-y

STUDY PROTOCOL

Effects of the SGLT-2 Inhibitor Empagliflozin on Renal Tissue Oxygenation in Non-Diabetic Subjects: A Randomized, Double-Blind, Placebo-Controlled Study Protocol

Marie-Eve Muller · Menno Pruijm · Olivier Bonny · Michel Burnier · Anne Zanchi

Multiparametric MRI in diabetic kidney disease

- 25 vs 25 diabetes and rapid or slow decline in eGFR (>4 or <2ml/min/yr) and 10 age-matched volunteers
- Baseline and 9/12 month MRI and measured GFR
- Can MRI differentiate rapid/slow groups at baseline?
- Can MRI distinguish mGFR trajectories at follow up?
- Which MRI parameter(s) are best?

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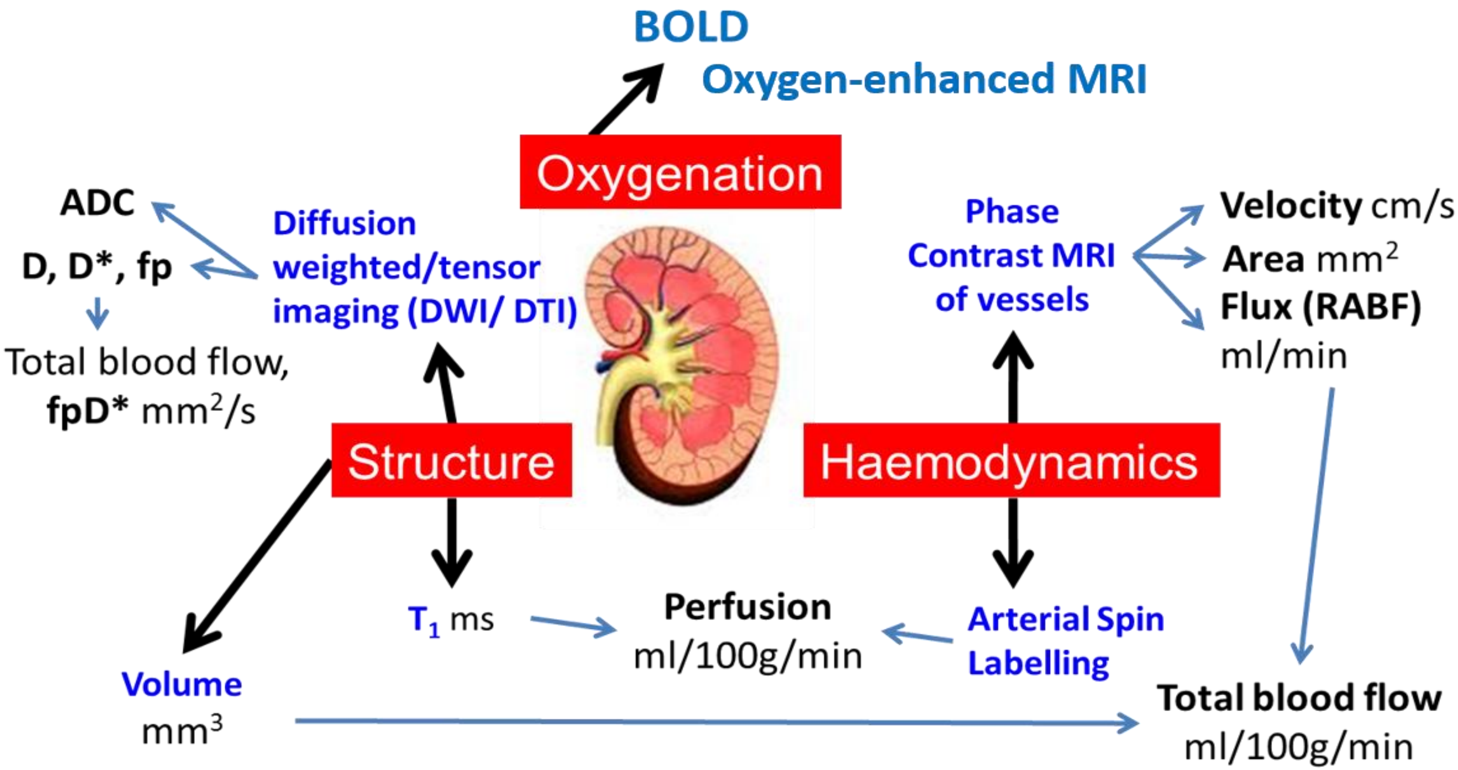
Multiparametric MRI in diabetic kidney disease



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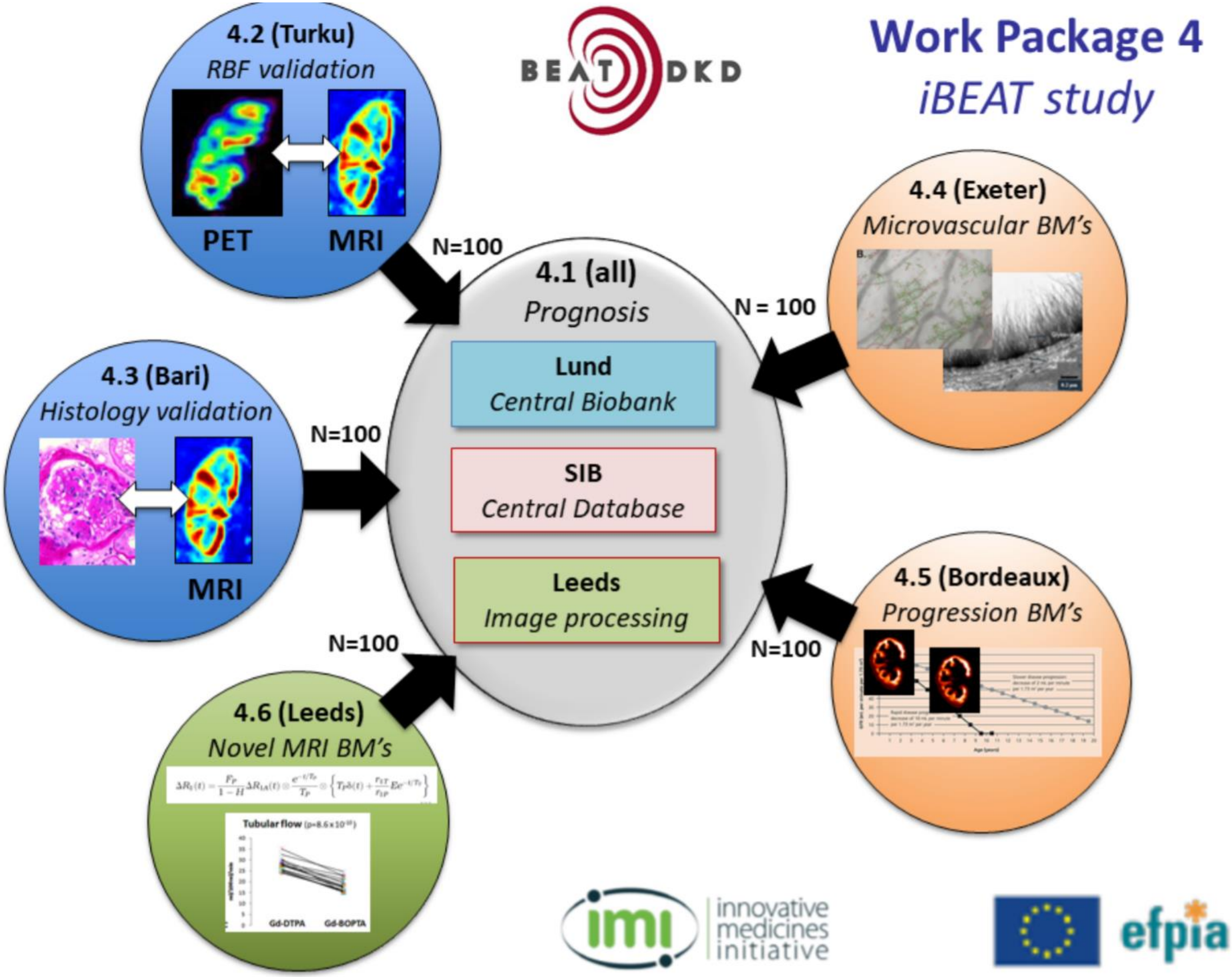
The Academy *of* Medical Sciences



Work Package 4
iBEAT study
BEAT DKD
4.2 (Turku)
RBF validation
PET
MRI
N=100
4.3 (Bari)
Histology validation
MRI
N=100
4.6 (Leeds)
Novel MRI BM's
Tubular flow
Gd-DTPA
Gd-BOPTA
N=100
4.1 (all)
Prognosis
Lund
Central Biobank
SIB
Central Database
Leeds
Image processing
4.4 (Exeter)
Microvascular BM's
N = 100
4.5 (Bordeaux)
Progression BM's
N=100
innovative medicines initiative
efpia

Application of MRI to DKD: evidence to date

- Results similar to CKD highlighting renal hypoxia
- Complements renal biopsy and other biomarkers
- Has unique benefits (reproducible, repeatable, non-contrast)
- Measuring multiple parameters serially will help
- How renal MRI is integrated into precision medicine approaches is the subject of ongoing research (eg DKD-MRI, iBEAT study

Questions?

https://www.renalmri.org/

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