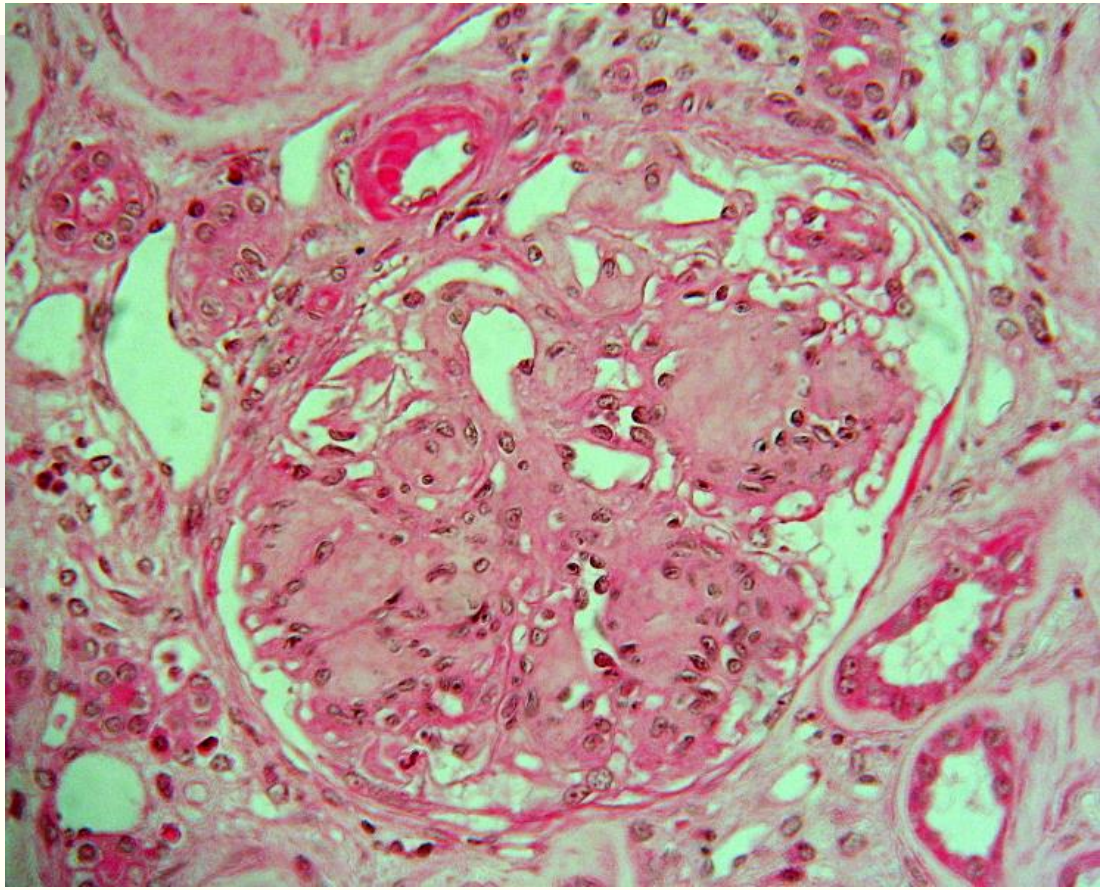
Biomarkers in Diagnosis and Progression of Diabetic Nephropathy



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Biomarker Definition (1998)

National Institutes of Health Biomarkers Definition Working Group

1. Objectively measure
2. It can evaluate a biological process , pathologic process, or pharmacologic responses to therapeutic intervention .
3. It provide a dynamic and powerful approach to understanding the spectrum of a disease from earliest manifestations to terminal stage.

Why This Review Is Important ?

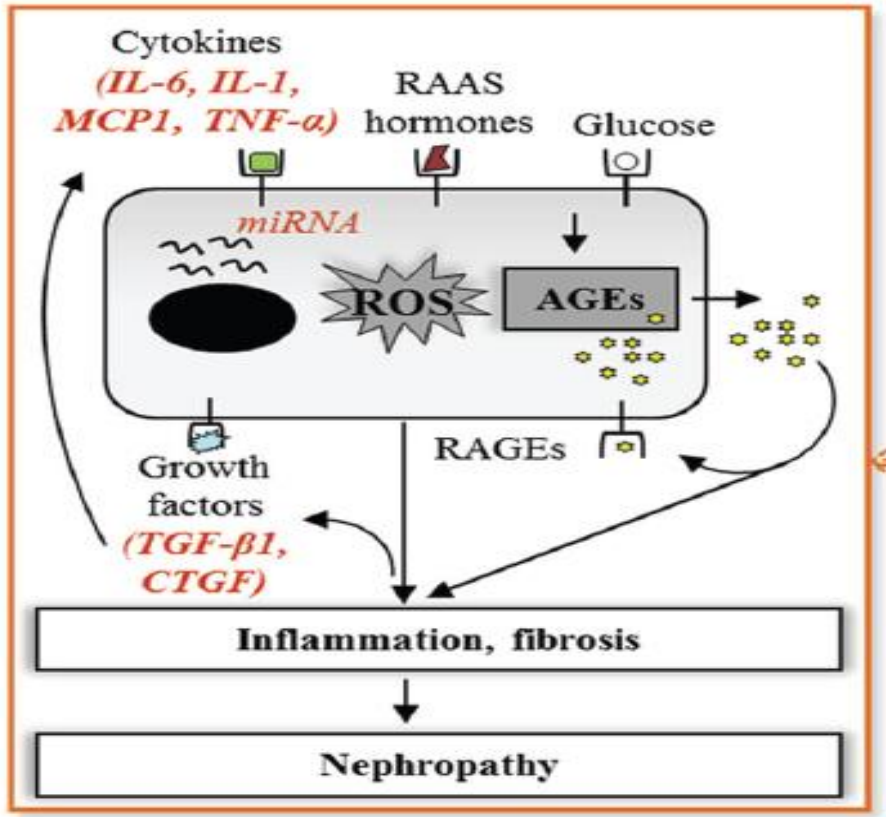
- Prevalent disease worldwide and a rise in incidence rate
- Albuminuria in not a sensitive and specific marker of diabetic nephropathy .
- Need to diagnose early risk of diabetic nephropathy
- Predict the progression of the disease
- Stratify the stage of disease
- Enabling targeted personalized therapy

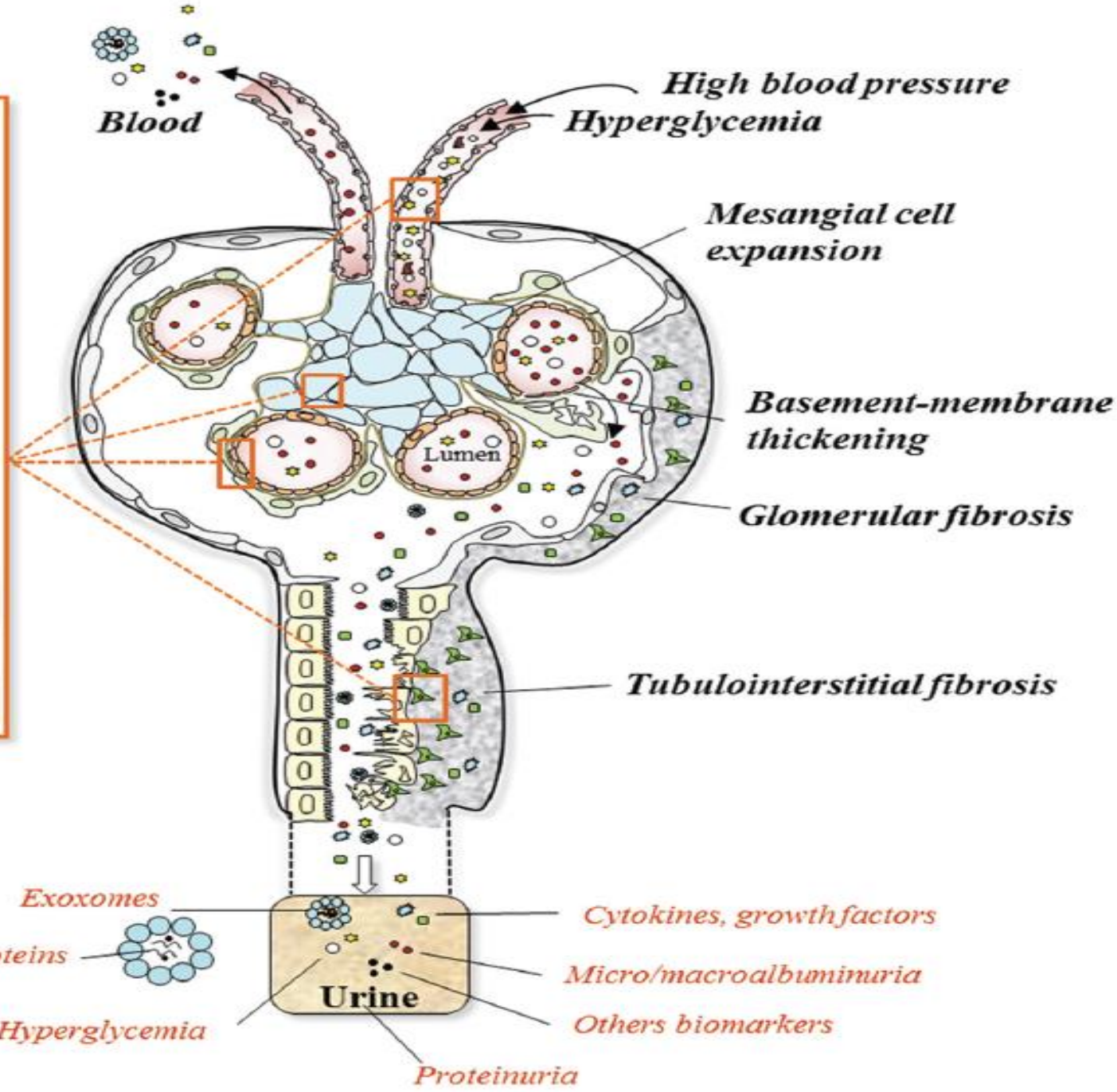
Currently Used Biomarkers And Predictive Value

- GFR :MDRD , Cockcroft gault, CKD EPI formula (creatinine based), measures GFR
- Limitations :Does not reflect the early stage of renal dysfunction, limited by variations in creatinine production
- BUN :Marker of kidney function
- Limitations :Blood volume ,febrile illness, high protein diet, alimentary tube feeding, gastrointestinal bleeding, dehydrated patients, and drugs. Liver dependent

Continued

- Cystatin C: As a marker of renal function ,a sensitive marker of diabetic nephropathy
- Limitations: High cost and not universally calibrated in every lab, thyroid function tests and corticosteroid consumptions have interfering effect
- Albuminuria: increased risk of cardiovascular and CKD progression
- Limitations : Some DN patients have not albuminuria, some times it is reversible and is not predictor of ESRD.



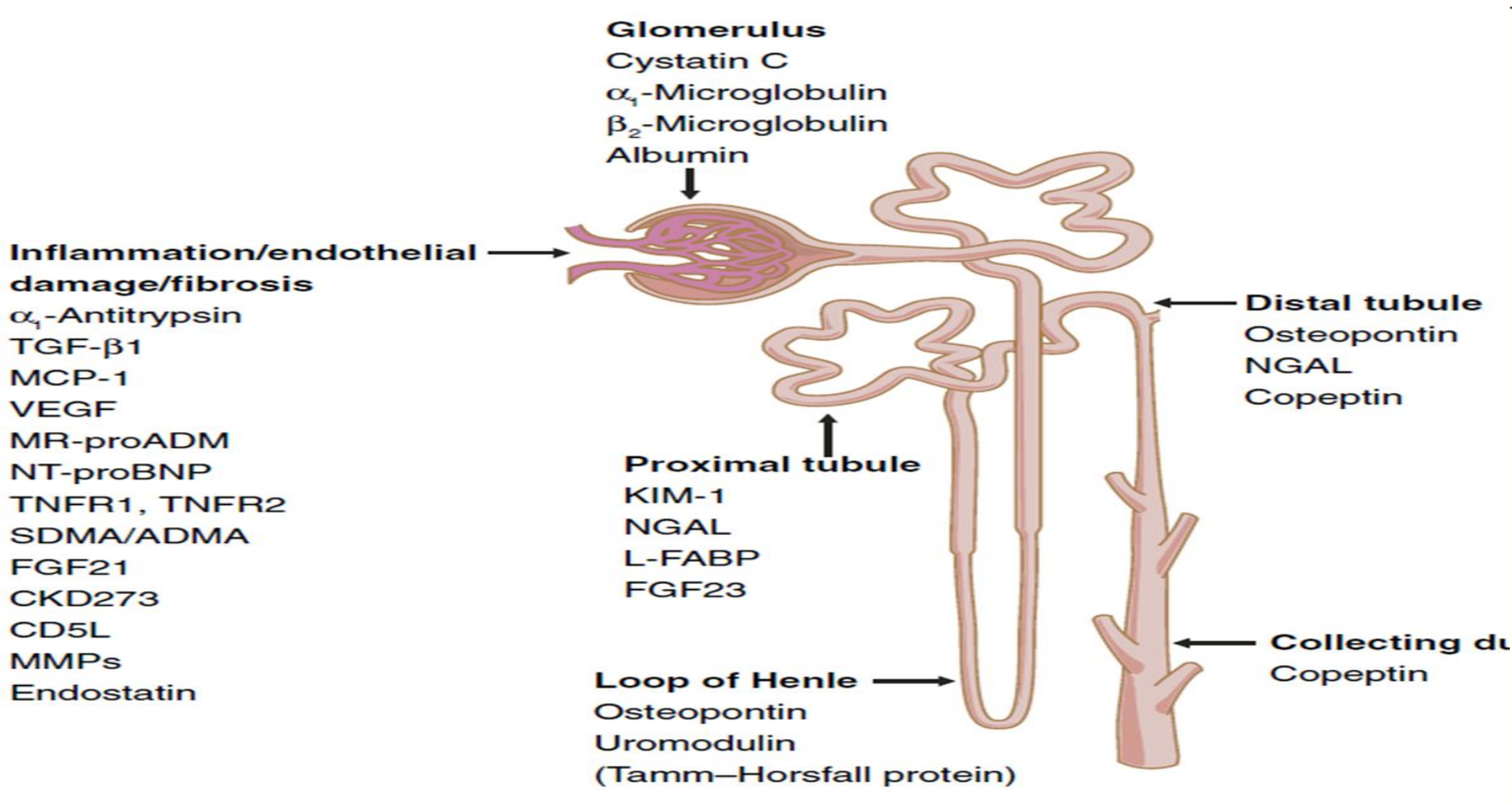


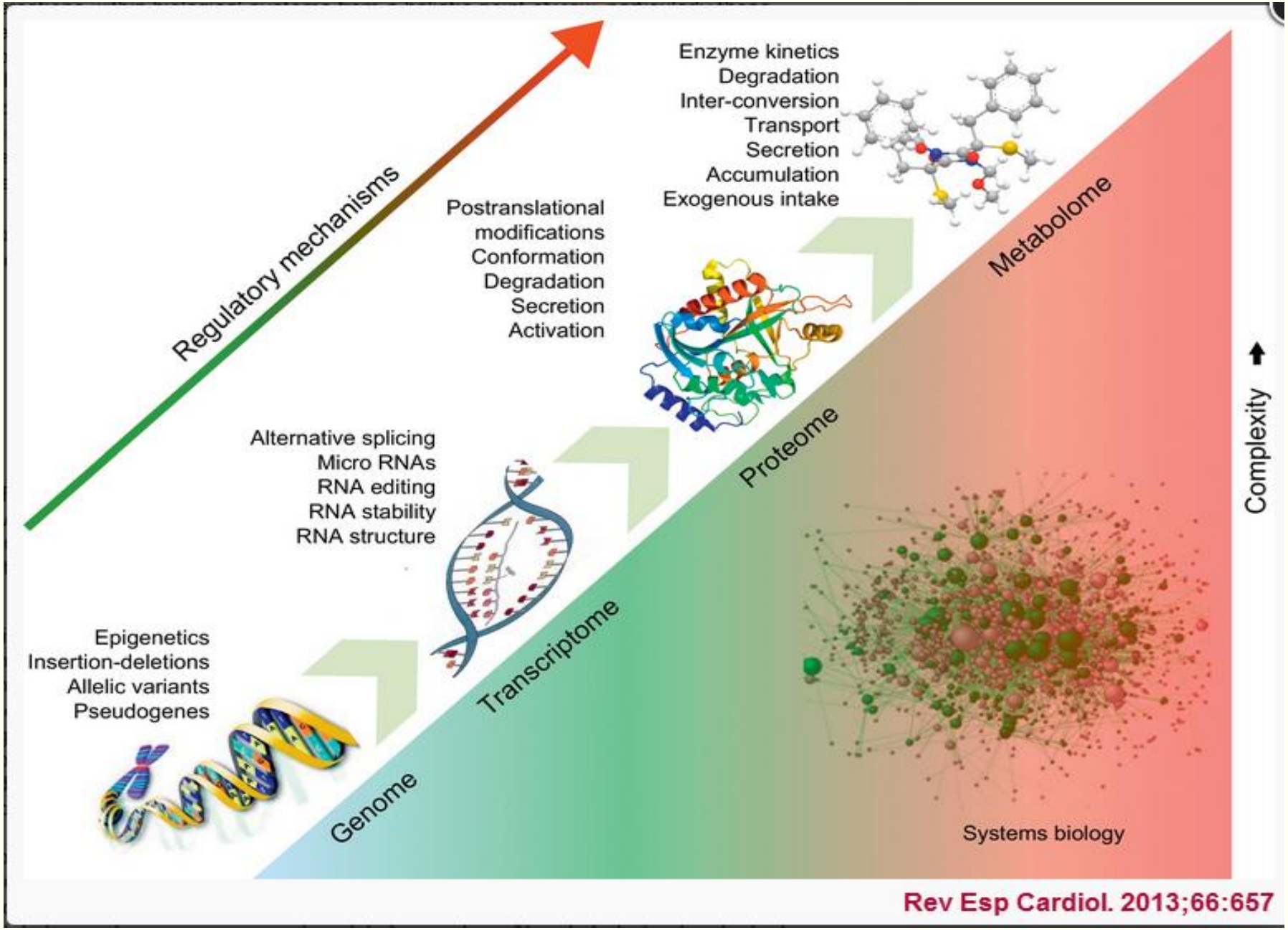
1-Hemodynamic Alterations

2- hyperglycemia

3- Inflammation

Site Of Origin Of Commonly Associated Biomarkers Predictive Of DKD.





Rev Esp Cardiol. 2013;66:657

Proteomics and Peptidomics

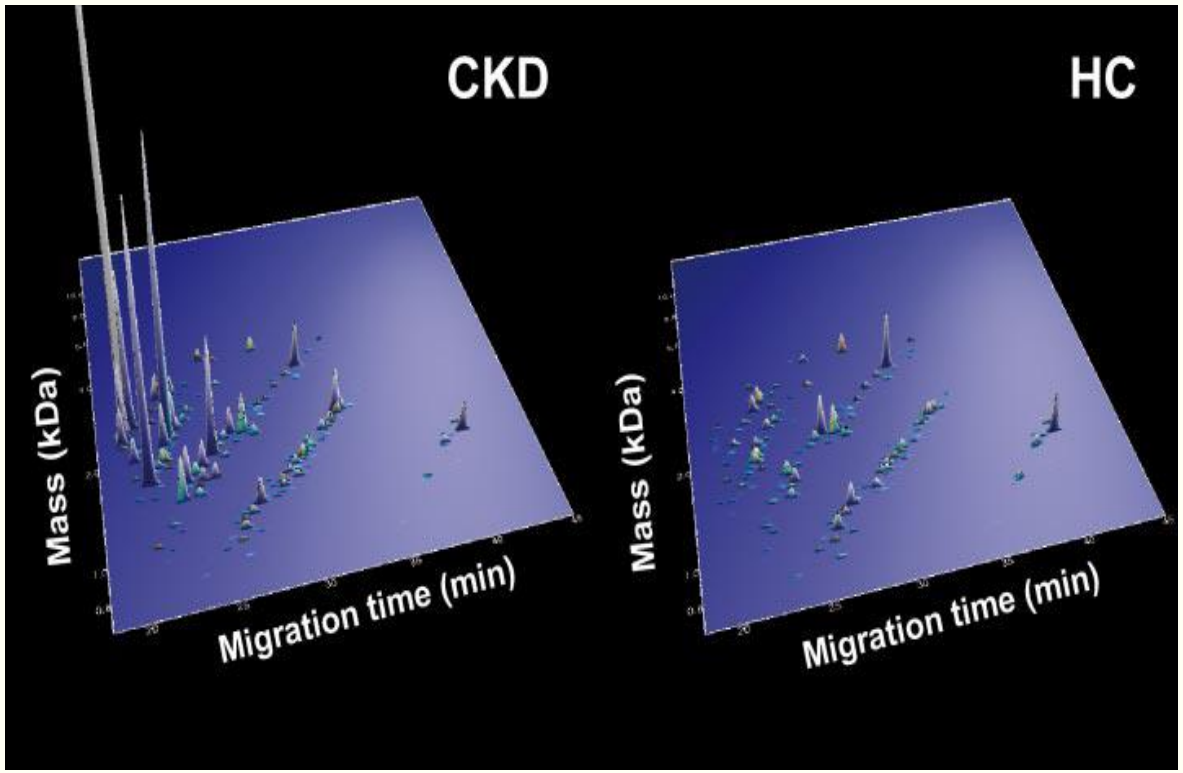
- Study of proteins is termed proteomics, whereas the study of naturally occurring peptides generated by endogenous protease activity is termed peptidomics.
- Urinary proteins and peptides originate from glomerular filtration , tubular secretion and epithelial cells shed from the kidney and urinary tract, exosomes, and secretions .
- Urine is a rich source of biomarkers for a wide range of diseases .
- Various techniques including two dimensional electrophoresis combined with mass spectrometry (MS) and/or immunochemical identification of proteins, (liquid chromatography coupled to mass spectrometry and surface-enhanced laser desorption/ionization mass spectrometry (SELDI-MS)

Naturally Occurring Human Urinary Peptides for Use in Diagnosis of Chronic Kidney Disease*[S]

Proteome analysis (800- 17000 Da)of urine samples from 230 patients with (different causes) CKD and 379 healthy control subjects.

A combination of the 273 CKD-specific biomarkers in a CKD-specific biomarker pattern would more accurately discriminate CKD patients from unaffected individuals.

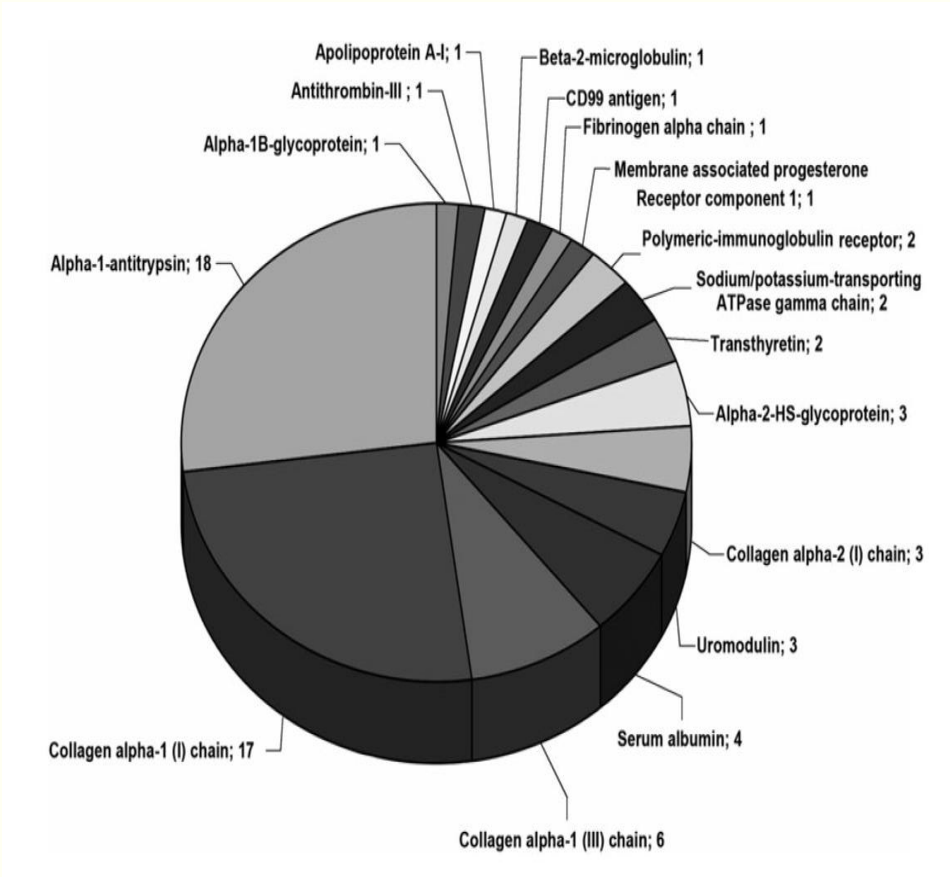
CKD is a conglomerate of diseases, and this fact is also reflected by the character of the biomarkers.



Good et al ,Molecular and cellular proteomics 2010

Multicentre prospective validation of a urinary peptidome-based classifier for the diagnosis of type 2 diabetic nephropathy

- Validation of CKD 273 in 9 centers for diabetic nephropathy (DN)
- PRIORITY aims to evaluate the early detection of DN inpatients with type 2 diabetes (T2D) using a urinary proteome based classifier (CKD273)
- 175 urine samples in 9 centers in type 2 diabetic patients in two group :No kidney involvement , Macroalbuminuric patients.
- This resulted in AUC values for the individual centers ranging between 0.9 and 1.0
- Prominent peptides are shown.



Siwy ,NDT, 2014

Urinary proteomics predict onset of microalbuminuria in normoalbuminuric type 2 diabetic patients, a sub-study of the DIRECT-Protect 2 study

- Post hoc analysis in the Diabetic Retinopathy Candesartan Trials
- 737 were analysed and 89 developed persistent microalbuminuria (12%) with a mean follow-up of 4.1 years.
- CKD273-classifier was an independent predictor of microalbuminuria and improved the risk prediction.

Model covariates[a]	HR in the model (95% CI; P-value)
CKD273-classifier	2.65 (1.55–4.55; 0.0004)
UAER	2.03 (1.73–2.38; <0.0001)
eGFR	1.40 (1.12–1.77; 0.004)
Age	1.40 (1.12–1.75; 0.004)
HDL cholesterol	0.74 (0.58–0.96; 0.02)

Hazard ratios from Cox-regression models with backward elimination with an event of persistent microalbuminuria as endpoint
(n = 723, events = 87)

Linhart et al NDT 2016 ,

BRIEF REVIEW www.jasn.org

Insights into Diabetic Kidney Disease Using Urinary Proteomics and Bioinformatics

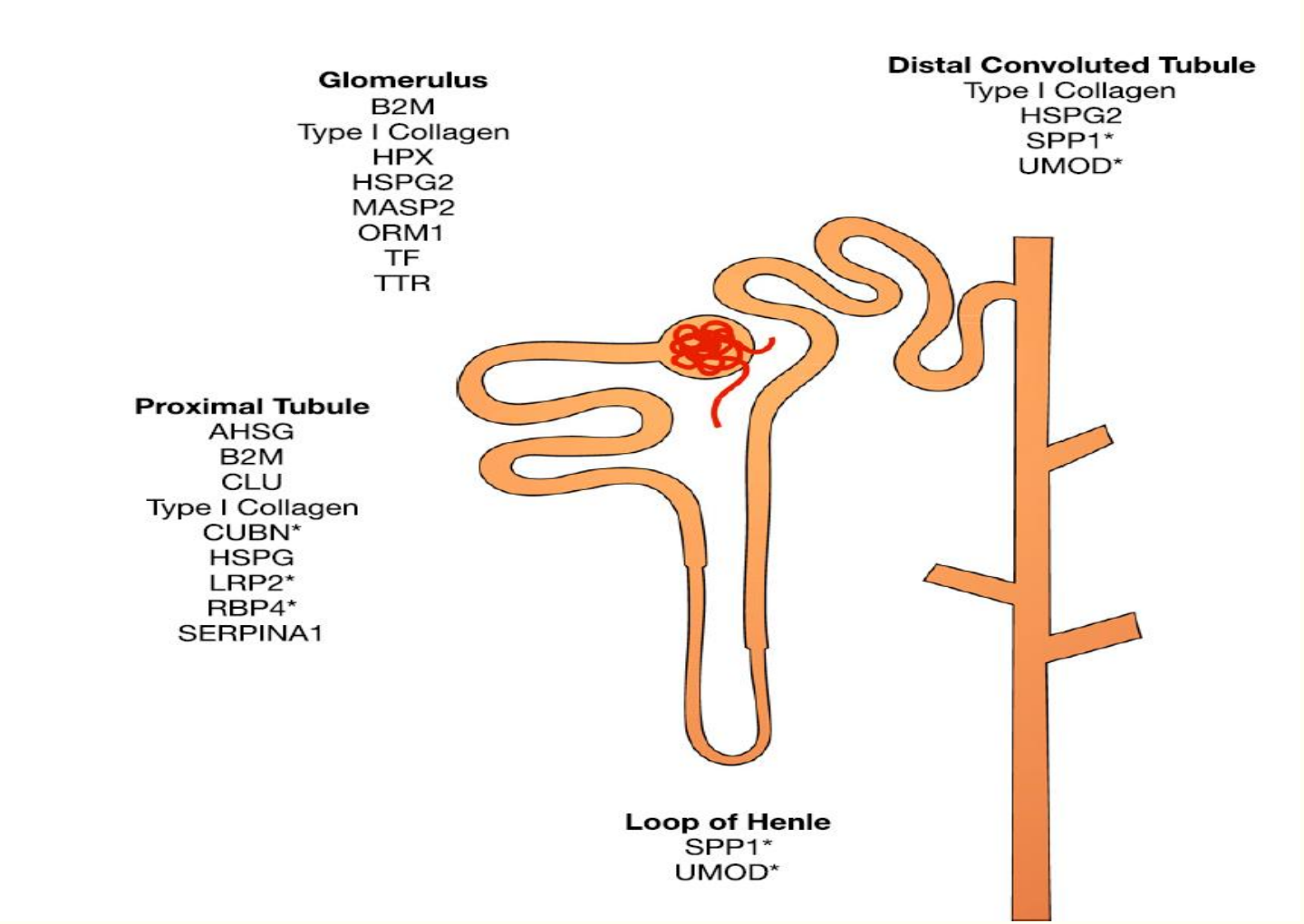
Julie A.D. Van,* James W. Scholey,*† and Ana Konvalinka*†

- The relationships between urinary proteins , their interaction and the underlying biological processes revealed by the analyses.
- 31 relevant urinary proteomic/peptidomics studies in diabetes were included.
- 76 different protein which was reported in DN and inputted in network analysis.

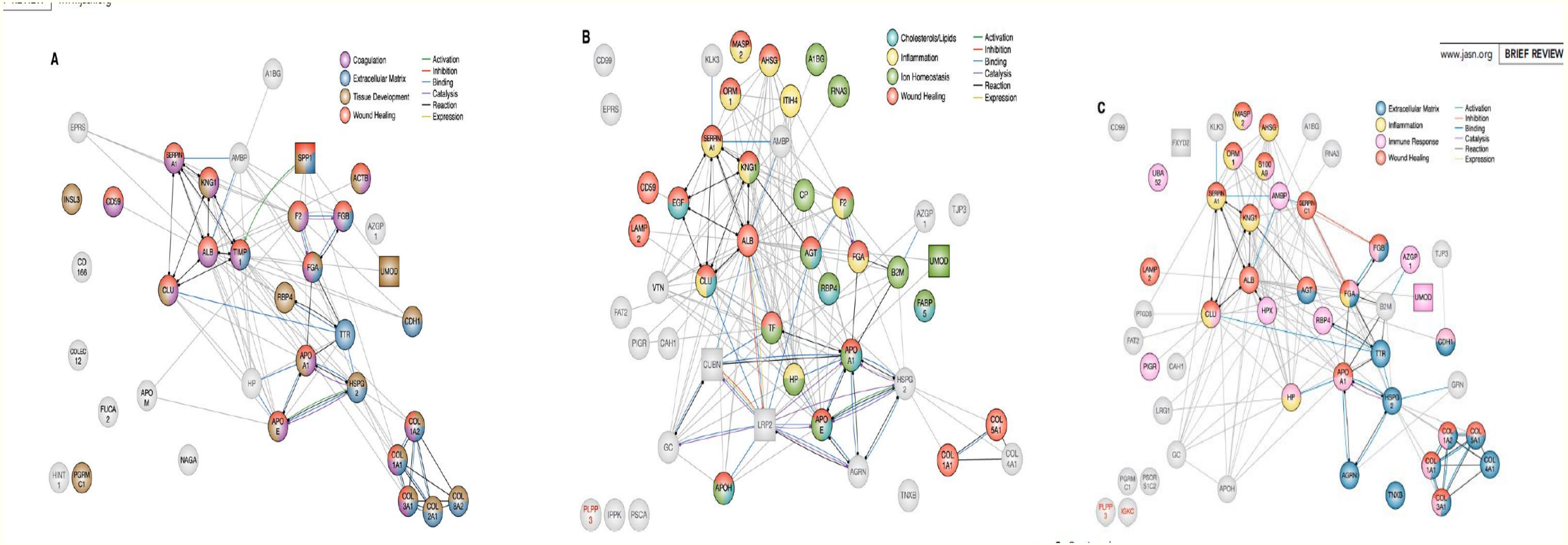
JASN 2017

Localization Of The Most Promising Urinary Markers Of Diabetic Kidney Disease In Different Nephron Segments

AHSG, a2-HSglycoprotein;
B2M, b2-microglobulin;
CLU, clusterin;
CUBN, cubilin;
HPX, hemopexin;
HSPG2, heparan sulfate proteoglycan; LRP2, megalin;
MASP2, mannan-binding lectin serine
protease 2 ;
ORM1, a1-acid glycoprotein 1;
RBP4, retinol-binding protein 4;
SERPINA1,a1-antitrypsin;
SPP1, osteopontin;
TF, transferrin;
TTR, transthyretin;
UMOD, uromodulin



Protein-protein interaction networks for differentially excreted proteins in diabetic kidney disease



Uncomplicated DM

Incipient DN

Overt DN

Table 1. Characteristics of promising markers for each stage of diabetic kidney disease

Stage of Diabetic Kidney Disease	Protein	Description	Direction of Urinary Excretion[a]	Nephron Segment	Biological Processes	Validated
Uncomplicated Diabetes	α_1-antitrypsin (SERPINA1)	40-kD serine protease inhibitor	↑ (9 of 9)	PT	Coagulation, inflammation	ELISA, SRM
	Clusterin (CLU)	50-kD nuclear form 75-kD secretory form	↑ (3 of 4)	PT	Complement activation, inflammation, lipid metabolism	ELISA
	Type I collagen (COL1A1/COL1A2)	>130-kD extracellular matrix protein	↓ (8 of 8)	NS	Extracellular matrix organization	None
	Heparan sulfate proteoglycan (HSPG2)	469-kD basement membrane protein	↓ (2 of 2)	NS	Blood vessel development, extracellular matrix organization	None
	Osteopontin (SPP1)	35-kD secreted phosphoprotein	↑ (1 of 1)	LoH, DCT*	Adhesion, tissue development	None
	Uromodulin (UMOD)	85-kD GPI-anchored glycoprotein	↓ (11 of 11)	LoH, DCT*	Tissue development	ELISA, SRM
Incipient Diabetic Nephropathy	α_1-acid glycoprotein 1 (ORM1)	24-kD positive acute-phase reactant	↑ (5 of 5)	G	Inflammation, immune system, transport	ELISA, immuno-turbidimetry
	Cubilin (CUBN)	399-kD endocytic receptor	↑ (1 of 1)	PT*	Endocytosis, lipid metabolism	None
	Haptoglobin (HP)	45-kD positive acute-phase reactant	↑ (2 of 4)	NS	Immune system response, inflammation	ELISA, SRM
	Megalin (LRP2)	522-kD endocytic receptor	↑ (1 of 1)	PT*	Endocytosis, tissue development	None
	Mannan-binding lectin serine protease 2 (MASP2)	76-kD serine protease	↑ (1 of 2)	NS	Complement activation, immune system response	SRM
	Transferrin (TF)	77-kD plasma carrier of iron	↑ (2 of 2)	G	Iron ion homeostasis, transport	SRM
Overt Diabetic Nephropathy	α_2-HS-glycoprotein (AHSG)	39-kD plasma carrier	↑ (5 of 5)	G, PT	Endocytosis, inflammation, tissue development	None
	β_2-microglobulin (B2M)	14-kD MHC class I component	↑ (5 of 5)	G, PT	Ion homeostasis, immune system response	None
	Hemopexin (HPX)	59-kD plasma carrier of heme	↑ (1 of 1)	G	Iron ion homeostasis, transport	None
	Retinol-binding protein 4 (RBP4)	23-kD plasma carrier of retinol	↑ (5 of 6)	PT*	Immune system response, tissue development, transport	ELISA
	Transthyretin (TTR)	55-kD homotetrameric plasma carrier of RBP4 and thyroxine	↓ (4 of 7)	PT	Extracellular matrix organization, transport	ELISA

Kidney Biomarkers and Decline in eGFR in Patients with Type 2 Diabetes

Katherine G. Garlo,[1,2] William B. White,[3] George L. Bakris,[4] Faiez Zannad,[5] Craig A. Wilson,[6] Stuart Kupfer,[6] Muthiah Vaduganathan,[7] David A. Morrow,[7] Christopher P. Cannon,[1,7] and David M. Charytan[1,2]

- Cystatin C, urinary kidney injury molecule–1,(uKIM-1), and urinary neutrophil gelatinase-associated lipocalin (UNGAL) in 5367 individuals with type 2 diabetes mellitus (EXAMINE Trial)
- eGFR decline occurred in 98 patients (1.8%) over a median of 1.5 years.
- The addition of **Cystatin C or biomarkers of tubular injury did not meaningfully improve** the prediction of eGFR decline beyond common clinical factors and routine laboratory data in a large cohort of patients with type 2 diabetes and recent acute coronary syndrome.

www.cjasn.org Vol 13 March, 2018

Prognostic Value of Tubulointerstitial Lesions, Urinary *N*-Acetyl-β-D-Glucosaminidase, and Urinary β2-Microglobulin in Patients with Type 2 Diabetes and Biopsy–Proven Diabetic Nephropathy

Koki Mise,[*†‡] *Junichi Hoshino,*[*] *Toshiharu Ueno,*[*] *Ryo Hazue,*[*] *Jumpei Hasegawa,*[*] *Akinari Sekine,*[*] *Keiichi Sumida,*[*] *Rikako Hiramatsu,*[*] *Eiko Hasegawa,*[*] *Masayuki Yamanouchi,*[*] *Noriko Hayami,*[*] *Tatsuya Suwabe,*[*] *Naoki Sawa,*[*] *Takeshi Fujii,*[§] *Shigeko Hara,*[*†] *Kenichi Ohashi,*[§‖] *Kenmei Takaichi,*[*†] *and Yoshifumi Ubara*[*†]

- 210 patients with type 2 diabetes and biopsy-proven DN managed from 1985 to 2011, Primary outcome ESRD, Follow-up 2.3 Yrs.

- Conclusion :Adding urinary NAG and b2-MG excretion to known promoters of progression did not improve prognostication, whereas adding the IFTA score did. The IFTA score may be superior to these tubulointerstitial markers for predicting the renal prognosis in advanced DN

Clin J Am Soc Nephrol 11: 593–601, 2016

Association of Urinary Biomarkers of Inflammation, Injury, and Fibrosis with Renal Function Decline: The ACCORD Trial

Girish N. Nadkarni, Veena Rao,† Faramarz Ismail-Beigi,‡ Vivian A. Fonseca,§ Sudhir V. Shah,‖ Michael S. Simonson,‡ Lloyd Cantley,† Prasad Devarajan,¶ Chirag R. Parikh,† and Steven G. Coca**

- MCP-1 is a member of the chemokine family that promotes recruitment and transformation of monocytes into macrophages.
- Kidney cells secrete MCP-1 in response to an inflammatory stimuli, and MCP-1 is known to be upregulated in kidney diseases as part of ongoing inflammation.
- uIL-18 is a proinflammatory cytokine of the IL-1 superfamily, and it is known to be upregulated in response to ischemia-reperfusion injury.
- uKIM-1 is a transmembrane glycoprotein that is expressed in the apical membrane of proximal tubular cells in

response to injury.

Clin J Am Soc Nephrol 11: 1343–1352, 2016

Continued

- They examined the association of four biomarker-to-creatinine ratio levels (monocyte
- Chemotactic protein-1, IL-18, kidney injury molecule-1, and YKL-40) with renal outcome.
- A nested case-control design in the Action to Control Cardiovascular Disease Trial
- 190 participants with >40% sustained eGFR decline over the 5-year
- Follow-up period to 190 participants with <10% eGFR decline in a 1:1 fashion
- Conclusion: Urinary monocyte chemotactic protein-1-to-creatinine ratio concentrations were strongly associated with sustained renal decline in patients with type 2 diabetes with preserved renal function.

Clin J Am Soc Nephrol 11: 1343–1352, 2016

Markers of early progressive renal decline in type 2 diabetes suggest different implications for etiological studies and prognostic tests development

Natalia Nowak[1,2,3], Jan Skupien[1,2,3], Adam M. Smiles[1], Masayuki Yamanouchi[1,2], Monika A. Niewczas[1,2], Andrzej T. Galecki[4,5], Kevin L. Duffin[6], Matthew D. Breyer[6], Nick Pullen[7], Joseph V. Bonventre[2,8] and Andrzej S. Krolewski[1,2]

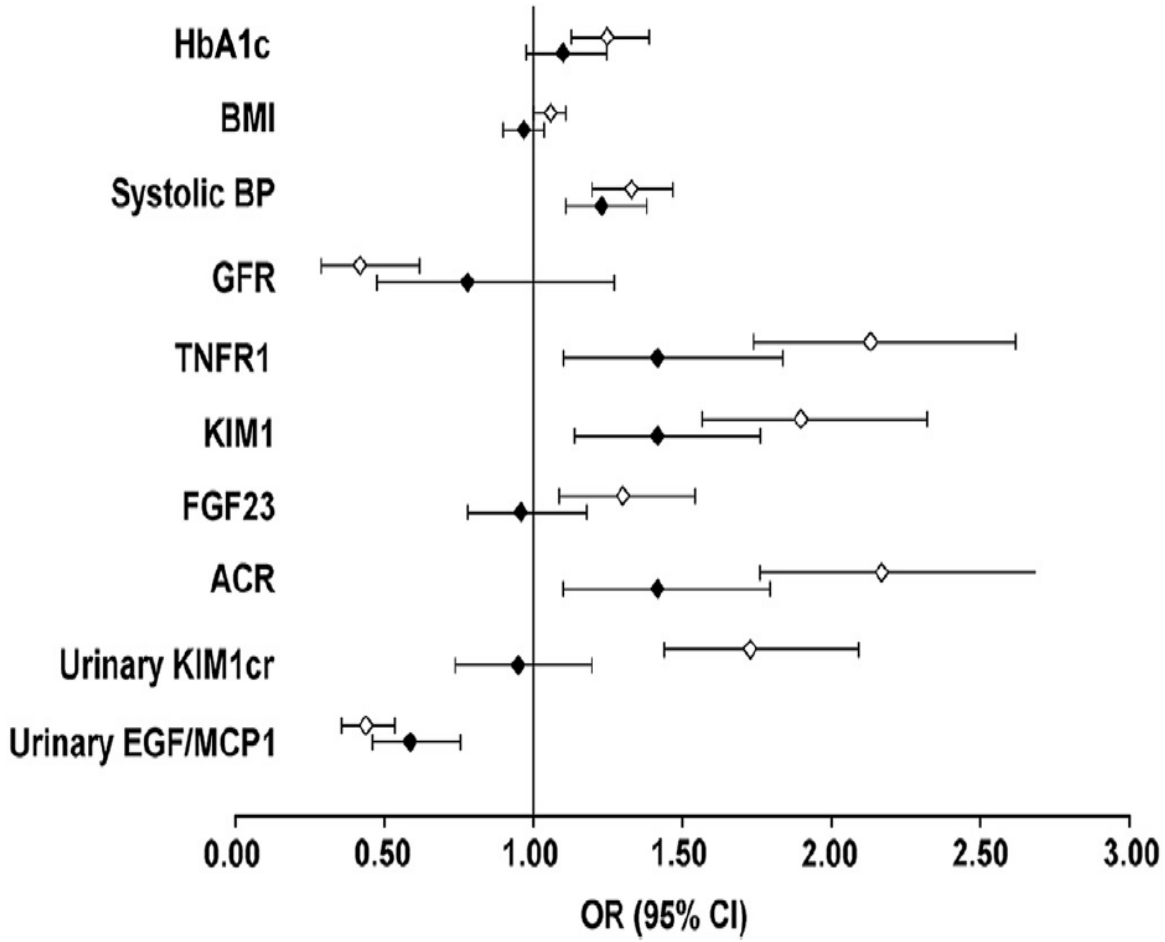
- Between 2003 and 2009, 1476 patients, 743 patients with albuminuria and 733 patients with normoalbuminuria
- 5-12 years follow-up with serial measurements of serum creatinine
- Biomarkers which were measured included : TNFR1, Fibroblast growth factor 23, Urinary and plasma KIM-1,Urine MCP-1, and EGF

Kidney international 2018

Prognostic Multimarker Test To Identify Patients At Risk Of Early Renal Decline

Conclusions :In addition to high systolic blood pressure and ACR, the risk of early renal decline was strongly associated with high circulating levels of TNFR1,KIM-1, and with a decreased urinary EGF/MCP-1 ratio

$$Score = ACR^{0.26} \times SBP^{2.35} \times TNFR1^{1.05} \times (KIM1 \times (MCP1/EGF))^{0.42} \times 10^{-3},$$



Kidney international 2018

Biomarkers of rapid chronic kidney disease progression in type 2 diabetes

A case–control design nested within a prospective cohort of patients.

eGFR 30–60 ml/min per 1.73m2. Within a 3.5-year period of Go-DARTS study patients,

154 had over a 40% eGFR decline and 153 controls maintained over 95% of baseline eGFR.

A total of 207 serum biomarkers were measured

Table 1 | Baseline demographics for cases and controls

	Control		Case	
	Frequency/median	Interquartile range	Frequency/median	Interquartile range
Female sex (%)	64.3	—	57.5	—
Age (years)	72	66–76	74	69–80
Diabetes duration (years)	7.2	3.5–11.0	9.1	5.1–15.4
Body mass index (kg/m^2)	29.5	26.1–34.4	30.6	27.1–34.8
Systolic blood pressure (mm Hg)	144.3	129.8–153.4	144.0	131.0–158.5
Diastolic blood pressure (mm Hg)	73.3	66.5–79.4	71.0	63.5–78.0
HbA1c (%)	7.1	6.4–8.2	7.3	6.5–8.4
Baseline eGFR (ml/min per 1.73 m^2)	51.3	44.9–54.6	48.2	40.5–54.8
Weighted average eGFR (ml/min per 1.73 m^2)	57.8	52.6–63.5	50.7	44.8–56.7
Insulin use (%)	25.3	—	30.7	—
Antihypertensive use (%)	95.5	—	96.1	—
Diabetic retinopathy (%)	55.2	—	74.5	—
Smoking (%)				
Current smoking	11.7	—	11.1	—
Ex-smoker	40.3	—	58.2	—
Never smoker	48.1	—	30.7	—
Prior CVD (%)	21.4	—	28.1	—
Albuminuria[a] (%)	18.8	—	45.1	—
Median follow-up (years)	5.8	5.5–6.2	3.2	2.2–5.7
Median time to caseness (years)	—	—	1.8	1.2–2.3

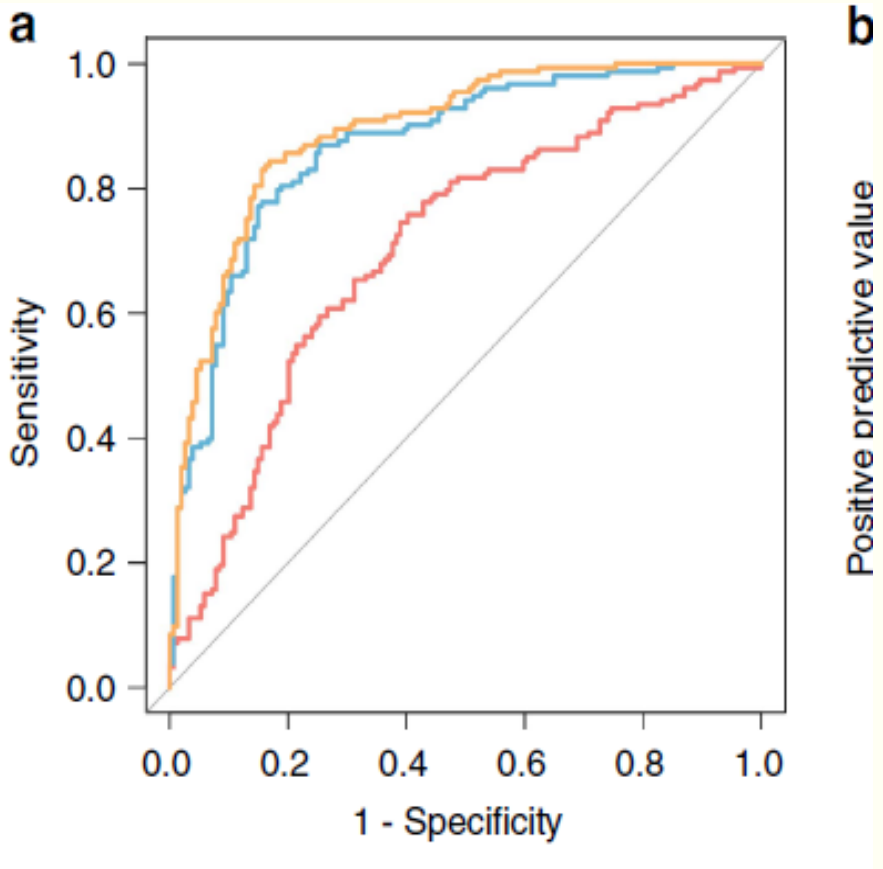
Abbreviations: CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c.
Data were complete except for body mass index (BMI) missing for 2 people, systolic blood pressure (SBP) missing for 3 people, diastolic blood pressure (DBP) missing for 2 people, hemoglobin A1c (HbA1c) missing for 1 individual, and drug treatment missing for 1 individual.
[a]Albuminuria status relates to the presence of microalbuminuria or macroalbuminuria at the time of sampling or any time in the prior 5 years.

Looker et al ,KI, 2015

Table 3 | Association of 14 biomarkers contributing to prediction of rapid progression in forward selection adjusted for each other and clinical covariates[a]

	Odds ratio per standard deviate	95% Confidence interval	*P*-value
Symmetric dimethylarginine/asymmetric dimethylarginine	8.36	3.83–20.40	<0.0001
Creatinine	3.52	1.54–8.76	0.0042
β2-Microglobulin	3.19	1.56–6.84	0.0019
Symmetric dimethylarginine	0.32	0.13–0.72	0.0075
α1 Antitrypsin (2)	2.05	1.38–3.14	0.0006
Kidney injury molecule-1	1.93	1.18–3.27	0.0111
Uracil	1.84	1.22–2.84	0.0046
N-terminal prohormone of brain natriuretic peptide	1.84	1.15–3.01	0.0123
C16-acylcarnitine	1.76	1.16–2.73	0.0090
Hydroxyproline[b]	1.73	1.12–2.72	0.0151
Fibroblast growth factor-21	1.69	1.06–2.75	0.0288
Fatty acid-binding protein heart[b]	0.63	0.38–1.02	0.0588
Creatine[b]	0.65	0.41–1.01	0.0590
Adrenomedullin	1.07	0.56–2.04	0.8370

[a]Clinical covariates included: age, sex, baseline estimated glomerular filtration rate (eGFR), albuminuria status, hemoglobin A1c (HbA1c), and use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers. [b]Biomarkers not statistically significant in univariate analyses adjusted only for clinical covariates.



Prediction of Declining Renal Function and Albuminuria in Patients with Type 2 Diabetes by Metabolomics

Anna Solini,[1] Maria Laura Manca,[1,2] Giuseppe Penno,[3] Giuseppe Pugliese,[4] Jeff E. Cobb,[3], and Ele Ferrannini[1,6]

- Screening metabolomics in serum and urine samples by GC/MS and UPLC/MS/MS* in 286 T2DM patients .
- Biomarker identification was performed by random forest using an eGFR <60 or an albumin/creatinine >30 mg/g as response variables
- At 3 years follow-up, eGFR had Declined by 16 [9] (median [IQR]) ml.Min-1.1.73m2 and ACR had increased by 41 [135] mg/G.
- The 5 serum metabolites best correlated with either eGFR<60 or ACR>30 at baseline were tested for their ability to improve clinical prediction.

*Ultrahigh performance liquid chromatography/Mass Spectroscopy(UPLC/MS/MS).

J Clin Endocrinol Metab 2015

- Sum of C- glycosyltryptophan, pseudouridine,and N-acetylthreonine (MetIndex) raised ROC to 0.739 (p0.0001).
- MetIndex also predicted ACR increase with an OR : 2.82.
- eGFR decline was predicted by the top MetaIndex quartile OR:5.48.
- Urine metabolites did not add significant predictivity.

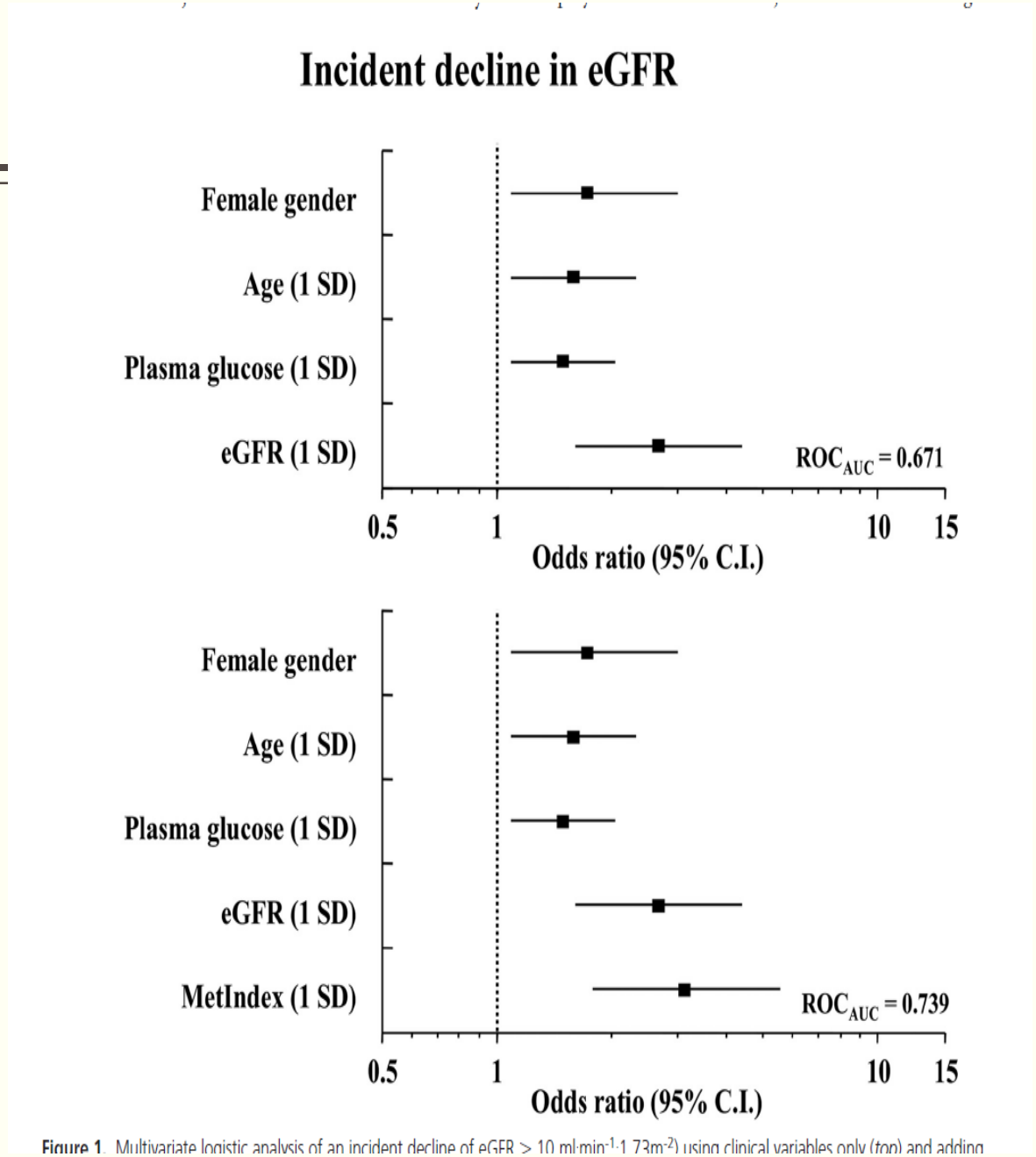


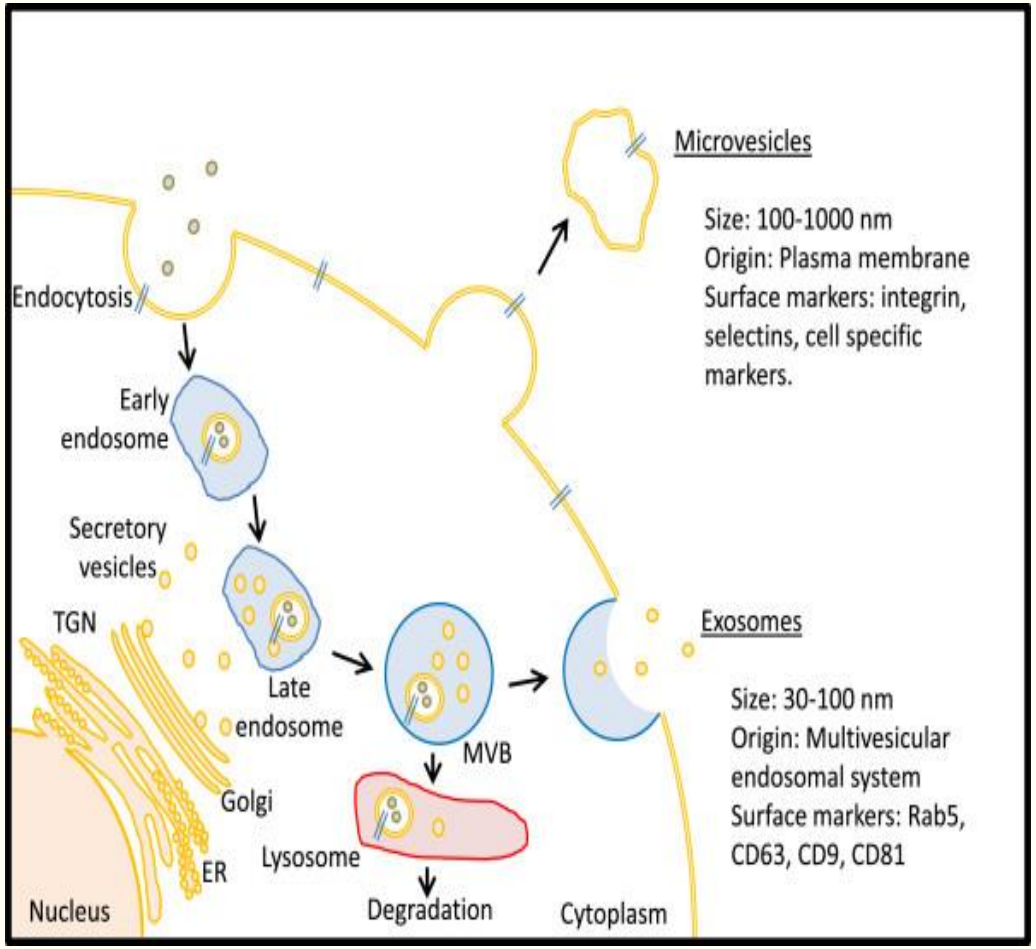
Figure 1. Multivariate logistic analysis of an incident decline of eGFR > 10 ml·min^{-1}·1.73m^{-2}) using clinical variables only (*top*) and adding

Urinary Microvesicles

- Urinary exosomes are membrane vesicles, secreted by tubular cells, with a diameter of 40–100 nm, while microparticles are membrane-shed vesicles with a size range between 100–1000 nm.
- Majority of microvesicles isolated from urine are thought to be exosome.
- Characterisations of these exosome-detected proteins under

normal and pathological conditions will help to define them

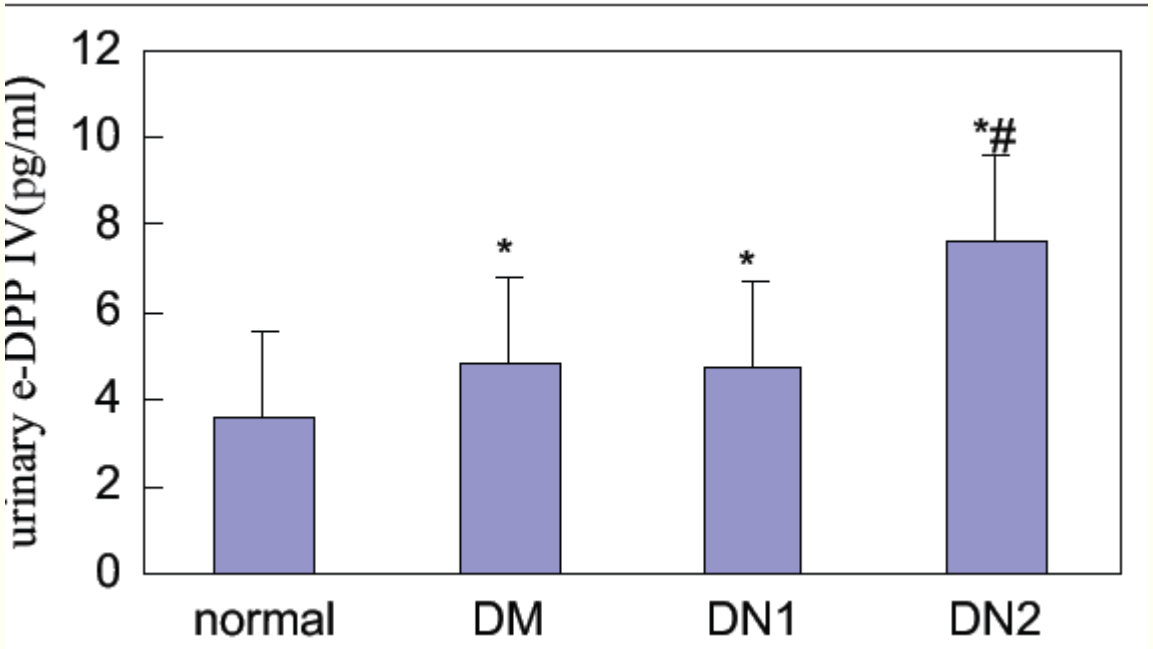
as biomarkers of diseases

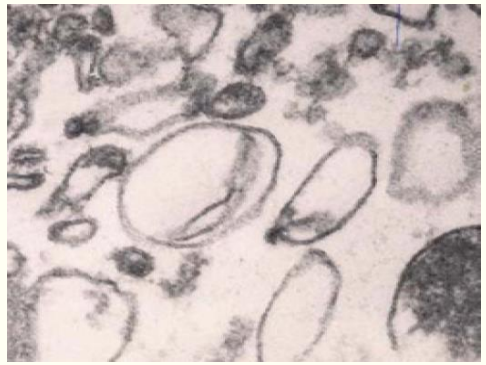


Diabetes & Vascular Disease Research ,2012

Dipeptidyl peptidase-IV is a potential molecular biomarker in diabetic kidney disease

- Dipeptidyl peptidase-IV (DPP IV) might be a urinary component of microvesicles.
- They studied the changes in microvesicle-dipeptidyl peptidase-IV (DPP IV) levels in 127 DM patients in different level of proteinuria.
- The urinary microvesicle-DPP IV level was positively correlated with UACR in patients with T2DM.
- Findings suggest that the urinary level of microvesicle-bound DPP IV is associated with the severity of DKD.





Ai-li Sun et al, Diabetes & Vascular Disease Research, 2012

Urinary Exosomal mRNA of WT1 as Diagnostic and Prognostic Biomarker for Diabetic Nephropathy

Hideharu Abe*, Akiko Sakurai*, Hiroyuki Ono, Sanae Hayashi, Sakiya Yoshimoto, Arisa Ochi, Sayo Ueda, Kenji Nishimura, Eriko Shibata, Masanori Tamaki, Fumi Kishi, Seiji Kishi, Taichi Murakami, Kojiro Nagai, and Toshio Doi

Urinary exosomes released by podocytes are microvesicles containing information of the originated cells.

Podocyte-derived signal transduction factors (PDSTFs) are good candidates to assess podocyte injuries.

Among PDSTFs in urinary exosomes, Wilms tumor 1 (WT1) levels reflected damage of diabetic glomeruli in the patients.

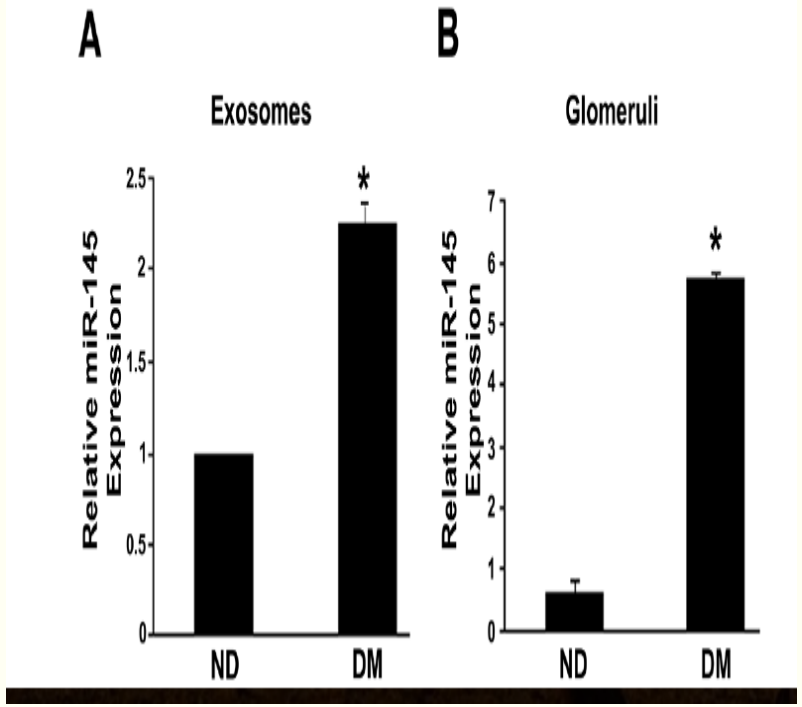
Urinary exosomal WT1 is a useful biomarker to predict future decline in renal function to improve risk stratification in patients with DN.

Journal of Medical Inves

Urinary Exosomal MicroRNAs in Incipient Diabetic Nephropathy

Federica Barutta[1*], Marinella Tricarico[1], Alessandro Corbelli[2,3], Laura Annaratone[4], Silvia Pinach[1], Serena Grimaldi[1], Graziella Bruno[1], Daniela Cimino[5], Daniela Taverna[5], Maria Chiara Deregibus[6], Maria Pia Rastaldi[2], Paolo Cavallo Perin[1], Gabriella Gruden[1]

- MicroRNAs (miRNAs), a class of small non-protein-encoding RNAs, regulate gene expression via suppression of target mRNAs.
- MiRNAs are present in body fluids in a remarkable stable form as packaged in microvesicles of endocytic origin, named exosomes.
- Exposure of cultured mesangial cells to high glucose increased miR-145 content in both mesangial cells and mesangial cells derived exosomes, providing a potential mechanism for diabetes-induced miR-145 overexpression.
- In conclusion, urinary exosomal miRNA content is altered in type 1 diabetic patients with incipient diabetic nephropathy and miR-145 may represent a novel candidate biomarker/player in the complication.



PLOS ONE,2013

PLOS | ONE

RESEARCH ARTICLE

Urinary Exosomal miRNA Signature in Type II Diabetic Nephropathy Patients

Denis Delić[1]*, Claudia Eisele[1], Ramona Schmid[1], Patrick Baum[1], Franziska Wiech[1], Martin Gerl[1], Heike Zimdahl[2], Steven S. Pullen[3], Richard Urquhart[4]

- Deregulated miR-320c, which might have an impact on the TGF-β-signaling pathway via targeting thrombospondin 1(TSP-1) shows promise as a novel candidate marker for disease progression in type II DN that should be evaluated in future studies.

March 2016

GEnetics of Nephropathy - an International Effort (GENIE) GWAS of Diabetic Nephropathy in the UK GoKinD and All-Ireland Cohorts

- The GENIE (GEnetics of Nephropathy an International Effort) consortium was initiated to perform the most comprehensive and well powered DN susceptibility genome wide association study (GWAS) analysis to date, using the largest collection of type 1 diabetics with and without kidney disease across four study cohorts.
- Through access to this data, they identified significant associations at susceptibility loci on chromosomes 9q, 11p, and 13q that have reproducibly been associated with diabetic nephropathy and that appear to be common in both T1D and T2D.

Pezzolesi et al., Kidney Int. 2011

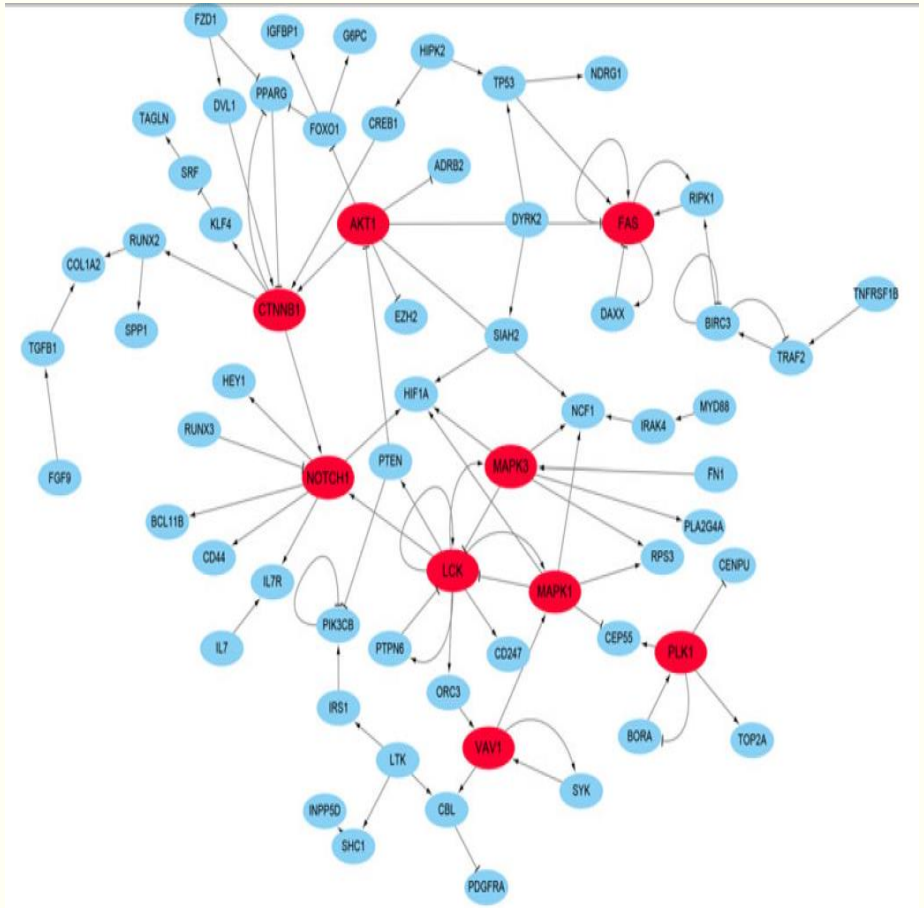
Nine hub genes as the potential indicator for the clinical outcome of diabetic nephropathy

Xiaoping Song[1*] | Min Gong[2*] | Yanping Chen[3] | Hui Liu[3] | Jun Zhang[4]

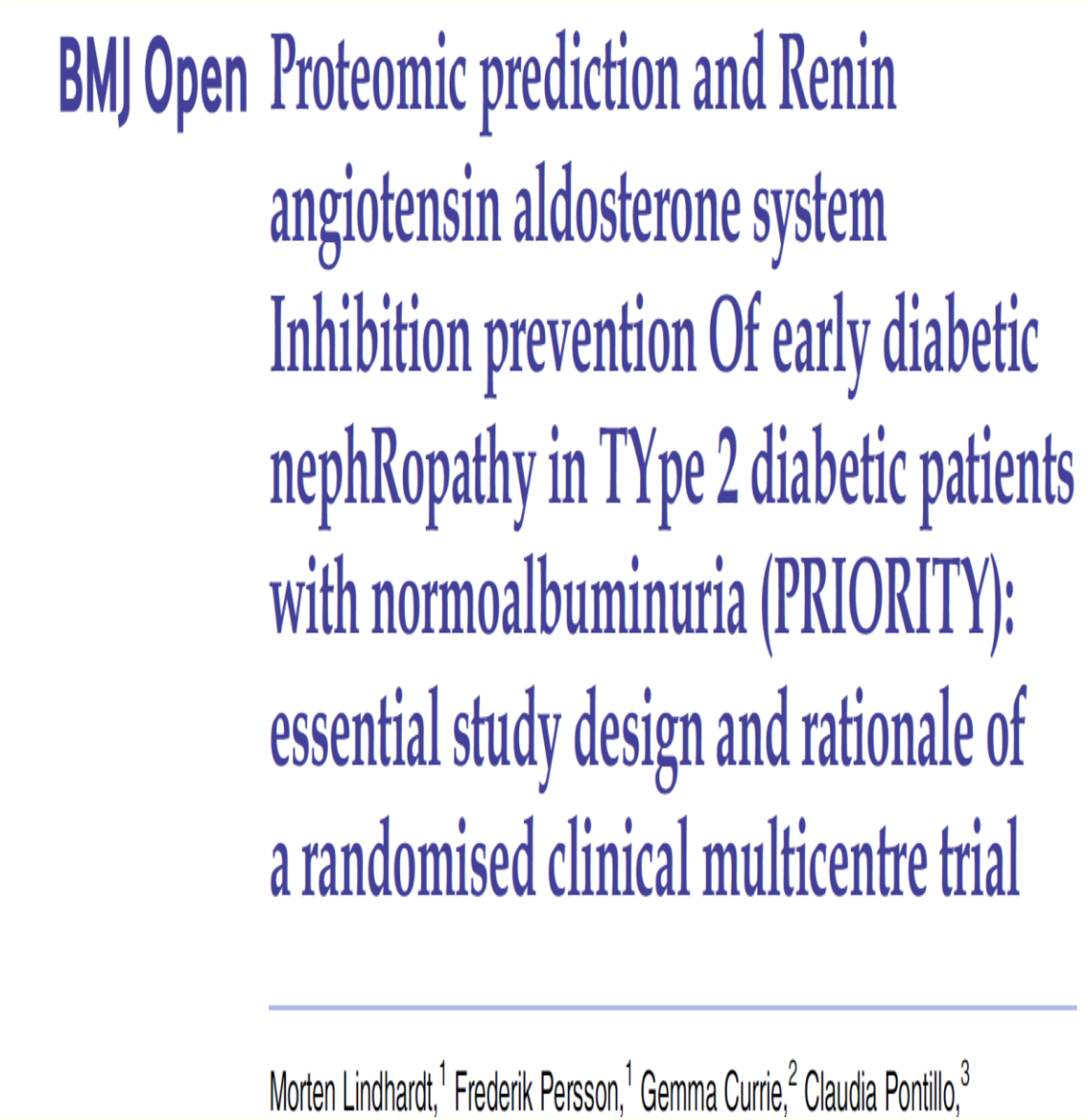
332 differentially expressed genes were identified between glomeruli tissues and tubulointerstitium tissues.

Nine hub genes were selected as the most potential biomarkers in the occurrence of DN.

Three genes VAV1, LCK, and Plk had the potential to serve as indicators for the occurrence and development of DN in clinical management.



J Cell Physiol. 2018;1–8.



- Multinational, multicenter investigator-initiated clinical trial.
- Aim to include more than 3000 participants with 3 years follow-up.
- Randomized, double masked intervention with spironolactone 25 mg, or placebo, in selected participants.
- Biomarker-directed therapy trial aiming at primary prevention of diabetic nephropathy.
- Validation of pre-existing urinary proteomics based on chronic kidney disease (CKD) risk classifier(CKD273).

The Effects Of Atrasentan On Urinary Metabolites In Patients With Type 2 Diabetes And Nephropathy

ΔAconitic acid

ΔCitric acid

ΔGlycolic acid

ΔHomovanillic acid

Δ2-ET-3-OH-Propionate

Δ3-OH-Isobutyrate

Δ3-OH-Isovalerate

Δ2-3-OH-Propionate

ΔUracil

ΔMetabolite index

Atrasentan therapy on a pre-specified panel of 13 urinary metabolites known to reflect mitochondrial function in patients with diabetic kidney disease.

doi: 10.1111/dom.12864

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ClinicalTrials.gov Identifier: NCT03105219

Recruitment Status ⓘ: Recruiting
First Posted ⓘ: April 7, 2017
Last Update Posted ⓘ: March 21, 2018

See **Contacts and Locations**

Sponsor:

Nanjing First Hospital, Nanjing Medical University

Information provided by (Responsible Party):

Shaoliang Chen, Nanjing First Hospital, Nanjing Medical University

Biomarkers in Use :Cystatin C , B2 Microglobin , N-acyl-β-D- glucosidase

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The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT02682563

Recruitment Status: Recruiting
First Posted: February 15, 2016
Last Update Posted: May 22, 2017

See **Contacts and Locations**

Sponsor:
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Collaborator:
AstraZeneca

Information provided by (Responsible Party):
M.H.H. Kramer, VU University Medical Center

Urinary NGAL, KIM-1

داستان پیل و خانه تاریک

همچنین هر یک به جزوی که رسید

فهم آن می‌کرد هر جا می‌شنید

از نظرگه گفتشان شد مختلف

آن یکی دالش لقب داد این الف

در کف هر کس اگر شمعی بدی

اختلاف از گفتشان بیرون شدی