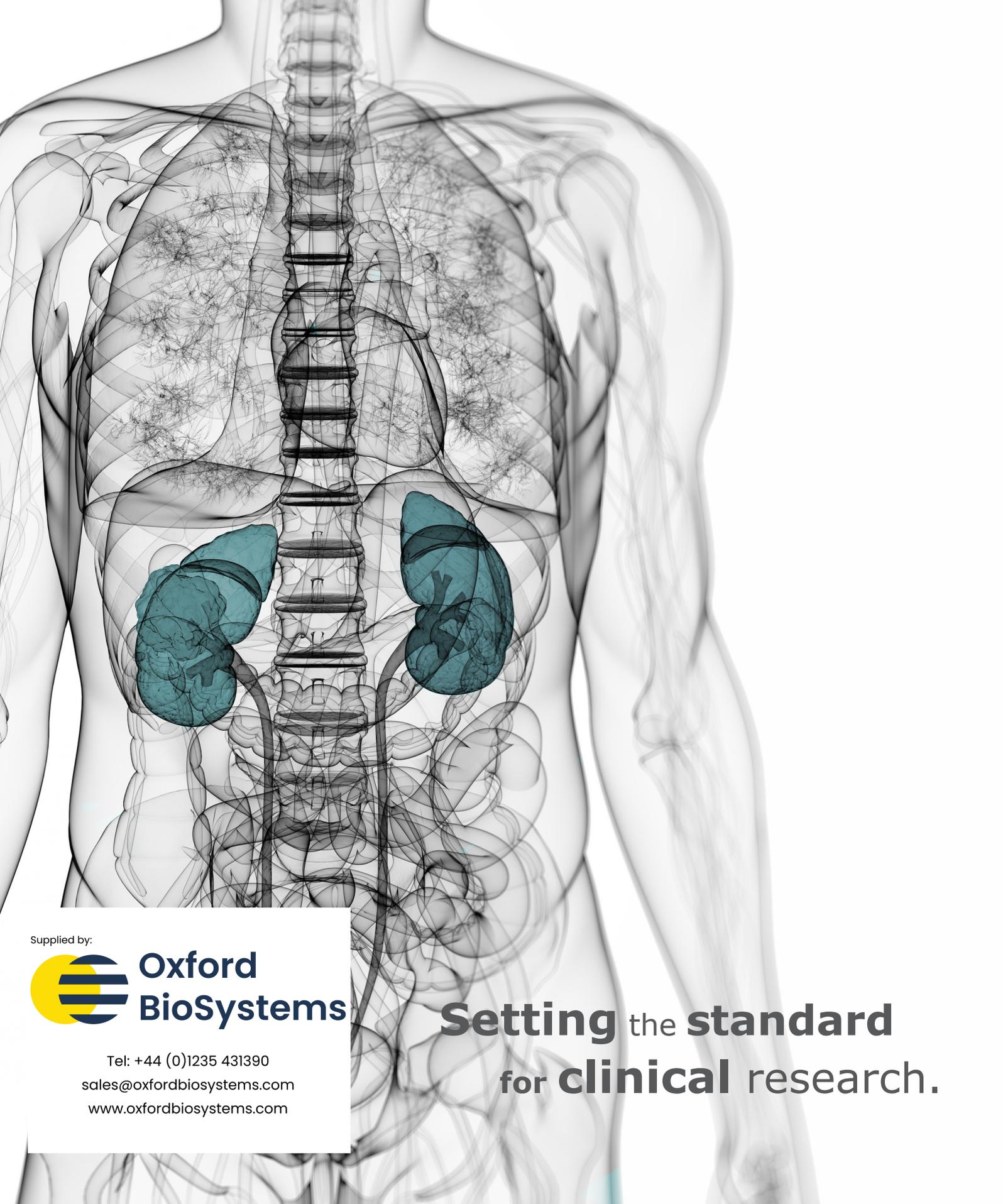


**BIOMARKERS IN
CLINICAL NEPHROLOGY**

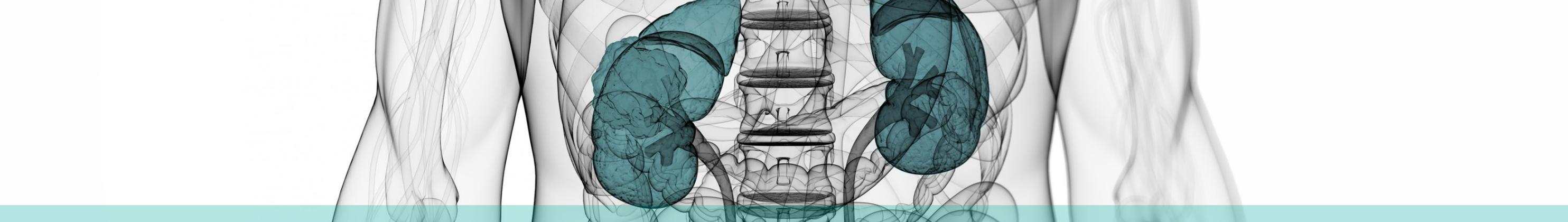


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Setting the **standard**
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FGF23

ENDOSTATIN

OPG

SCLEROSTIN

FGF23

FOR RISK PREDICTION IN CHRONIC RENAL INSUFFICIENCY AND TO DETERMINE CARDIOVASCULAR RISK IN CKD

Association of Fibroblast Growth Factor 23 with Atrial Fibrillation in Chronic Kidney Disease, From the Chronic Renal Insufficiency Cohort Study.

Mehta et al., *JAMA Cardiology*, 2016; 1(5):548-556.

"Elevated FGF23 is independently associated with prevalent and incident atrial fibrillation in patients with mild to severe CKD."

Fibroblast growth factor 23 in patients with acute dyspnea: Data from the Akershus Cardiac Examination (ACE) 2 Study. *

Lyngbakken et al., *Clin Biochem*, 2017; pii: S0009-9120(17):30670-30677.

"Circulating FGF23 concentrations provide incremental prognostic information to established risk indices in patients with acute dyspnea."

FGF23 and vitamin D metabolism in chronic kidney disease – mineral bone disorder. *

Piec et al., *Bone Abstracts*, 2016; 5:P469.

"cFGF23 is raised in patients with CKD as a compensatory response to hyperphosphatemia or phosphate overload."

Renal and Extrarenal Effects of Fibroblast Growth Factor 23.

Vervloet, *Nature Reviews*, 2019; *Nephrology* 1(2):109-120.

".. FGF23 is also a valuable biomarker as it predicts risk of a wide variety of clinical events, in particular heart failure."

ENDOSTATIN

FOR THE DETECTION OF ADVANCED MICROVASCULAR KIDNEY DAMAGE AND THE PROGRESSION OF KIDNEY DISEASE

The association between endostatin and kidney disease and mortality in patients with type 2 diabetes.

Carlsson et al., *Diabetes Metab*, 2016; 42(5):351-357.

"In patients with T2D, circulating endostatin levels can predict the progression of kidney disease and mortality independently of established kidney disease markers."

Endostatin in chronic kidney disease: Associations with inflammation, vascular abnormalities, cardiovascular events and survival. *

Kanbay et al., *Eur J Intern Med*, 2016; 33:81-87.

"Endostatin levels are independently associated with incident CVE in CKD patients."

Elevated plasma levels of endostatin are associated with chronic kidney disease.

Chen et al., *Am J Nephrol*, 2012; 35(4):335-340.

"These data indicate that elevated plasma endostatin is strongly and independently associated with CKD."

Circulating endostatin and the incidence of heart failure.

Ruge et al., *Scand Cardiovasc J*, 2018; 52(5):244-249.

"Higher serum endostatin was associated with left ventricular dysfunction and an increased heart failure risk in two community-based cohorts of elderly."

OSTEOPROTEGERIN (OPG)

FOR THE PREDICTION OF CARDIOVASCULAR MORTALITY

Osteoprotegerin concentrations in patients with suspected reversible myocardial ischemia: Observations from the Akershus Cardiac Examination (ACE) 1 Study. *

Røysland et al., *Cytokine*, 2015; 73:122-127.

"In a large cohort of kidney transplant patients [...], OPG was independently associated with renal events, CV events and mortality."

Osteoprotegerin as a predictor of renal and cardiovascular outcomes in renal transplant recipients: follow-up data from the ALERT study. *

Svensson et al., *Nephrol Dial Transplant*, 2012; 27:2571-2575.

"In a large cohort of kidney transplant patients with long-term follow-up, OPG was independently associated with renal events, CV events and mortality."

Serum osteoprotegerin is a predictor of progression of atherosclerosis and coronary calcification in hemodialysis patients. *

Kurnatowska et al., *Nephron Clin Pract*, 2011; 117(4):297-304.

"The plasma level of OPG could serve as a surrogate marker of progression of atherosclerosis and calcification in patients with end-stage renal disease."

Serum osteoprotegerin and renal function in the general population: the Tromsø Study.

Vik et al., *Clin Kidney J*, 2017; 10(1):38-44.

"Our findings imply that the association between OPG and eGFR varies with age and renal function."

SCLEROSTIN

FOR THE DIAGNOSIS OF HIGH BONE TURNOVER IN CKD AND THE PREDICTION OF CORONARY ARTERY CALCIFICATION

Circulating levels of sclerostin but not DKK1 associate with laboratory parameters of CKD-MBD. *

Behets et al., *PLOS ONE*, 2017; 12(5)

"Sclerostin, as opposed to DKK1, may qualify as a biomarker of CKD-MBD, particularly in dialysis patients."

Sclerostin serum levels correlate positively with bone mineral density and microarchitecture in haemodialysis patients.

Cejka et al., *Nephrol Dial Transplant*, 2012; 27:226-230.

"Dialysis patients had significantly higher Sclerostin levels than controls."

Serum Sclerostin and adverse outcomes in nondialyzed chronic kidney disease patients. *

Kanbay et al., *J Clin Endocrinol*, 2014; 99(10):E1854-E1861.

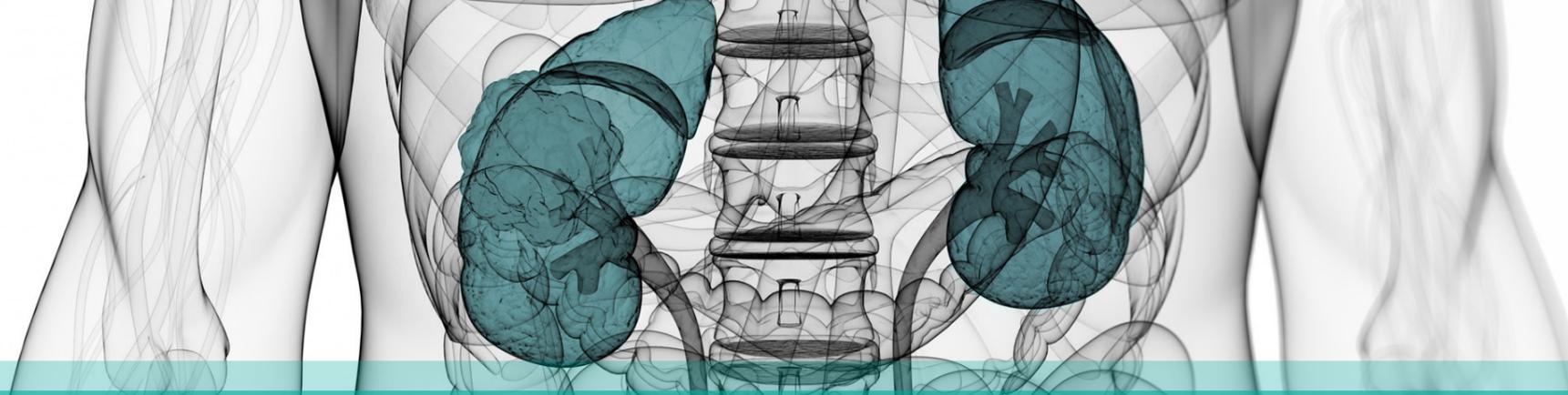
"Serum sclerostin values are associated, even after multiple adjustments, with fatal and nonfatal cardiovascular events in a nondialyzed CKD population."

Relationship between plasma levels of sclerostin, calcium-phosphate disturbances, established markers of bone turnover, and inflammation in haemodialysis patients.

Pietrzyk et al., *Int Urol Nephrol*, 2019; 51(3):519-526.

"Increased circulating sclerostin levels seem to reflect slower bone turnover in HD patients. Low levels of sclerostin are associated with vitamin D deficiency and good phosphates alignment."

* measured with Biomedica ELISA



VANIN-1

ANGIPOIETIN-2

BIG ENDOTHELIN

PERIOSTIN

VANIN-1

A MARKER FOR DRUG-INDUCED & SPONTANEOUS ACUTE KIDNEY INJURY AND OBSTRUCTIVE & DIABETIC NEPHROPATHY

A Novel Biomarker for Acute Kidney Injury, Vanin-1, for Obstructive Nephropathy: A Prospective Cohort Pilot Study.

Washino et al., *Int J Mol Sci*, 2019; 20(4).

"Urinary Vanin-1 is a useful biomarker to detect and monitor the clinical course of obstructive nephropathy."

Urinary Vanin-1 as a Novel Biomarker for Early Detection of Drug-Induced Acute Kidney Injury.

Hosohata et al., *J Pharm Exp Ther*, 2002; 341(3):656-662.

"... compared with urinary Kim-1 and NGAL, urinary vanin-1 is an earlier and equally sensitive biomarker for drug-induced AKI."

Vanin-1: A Potential Biomarker for Nephrotoxicant-Induced Renal Injury.

Hosohata et al., *Toxicology*, 2011; 290(1):82-88.

"These results suggest that vanin-1 is a useful and rapid biomarker for renal tubular injury induced by organic solvents."

Early Detection of Renal Injury Using Urinary Vanin-1 in Rats with Experimental Colitis.

Hosohata et al., *J App Tox*, 2014; 34(2):184-190.

"Compared with Kim-1 and MCP-1, vanin-1 might be an earlier biomarker for the detection of renal injury in rats with experimental colitis."

ANGIPOIETIN-2

FOR THE PREDICTION OF ALL-CAUSE MORTALITY IN KIDNEY TRANSPLANT RECIPIENTS AND PREDICTING ADVERSE CLINICAL OUTCOMES IN DIABETIC PATIENTS

Angiotensin-2, Renal Deterioration, Major Adverse Cardiovascular Events and All-Cause Mortality in Patients with Diabetic Nephropathy.

Tsai et al., *Kidney Blood Press Res*, 2018; 43(2):545-554.

"Angpt2 is an independent predictor of adverse clinical outcomes in diabetic patients."

Circulating Angiotensin-2 levels predict mortality in kidney transplant recipients: a 4-year prospective case-cohort study.

Molnar et al., *Transpl Int*, 2014; 27(6):541-552.

"... circulating Angpt2 was an independent predictor of all-cause mortality in stable, prevalent kidney transplant recipients."

Circulating angiotensin-2 levels increase with progress of chronic kidney disease.

David et al., *Nephrol Dial Transplant*, 2010; 25:2571-2579.

"Circulating Ang-2, a putative marker and potential mediator of accelerated atherosclerosis, is inversely related to GFR and increases with advanced CKD."

The interaction between fluid status and angiotensin-2 in adverse renal outcomes of chronic kidney disease.

Tsai et al., *PLoS One*, 2017; 12(3):e173906.

"Fluid overload and Angpt2 might have a synergistic effect on adverse renal outcomes in CKD patients."

BIG ENDOTHELIN

FOR IMPROVED RISK STRATIFICATION IN PATIENTS REFERRED FOR CORONARY ANGIOGRAPHY, CARDIOVASCULAR DEATH AND CHRONIC HEART FAILURE

Renal function, N-terminal Pro-B-Type natriuretic peptide, propeptide big-endothelin and patients with heart failure and preserved ejection fraction. *

Gergei et al., *Peptides*, 2019; 111:112-117.

"In general, NT-proBNP is a good indicator of suspected heart failure. While for NT-proBNP different cut-off points have to be considered in the diagnosis of HFpEF, a single cut-off point of Big-ET-1 was appropriate in the diagnosis of HFpEF, regardless of the presence or absence of CKD. An additional measurement of Big-ET-1 improves the diagnosis of HFpEF in patients with chronic kidney disease."

Association of Big Endothelin-1 with Coronary Artery Calcification. *

Qing et al., *PLoS ONE*, 2015; 10(11):e0142458.

"The data firstly demonstrated that the plasma big ET-1 level was a valuable independent predictor for CAC in our study."

Propeptide Big-Endothelin, N-Terminal-pro Brain Natriuretic Peptide and Mortality. The Ludwigshafen Risk and Cardiovascular Health (LURIC) Study. *

Gergei et al., *Biomarkers*, 2017;

22(3-4):315-320.

"Big-ET-1 improves risk stratification in patients referred for coronary angiography."

PERIOSTIN

A BIOMARKER FOR SEVERITY, PROGRESSION AND RESPONSE TO THERAPY IN HUMAN KIDNEY DISEASE ASSOCIATED TO HYPERTENSION

Identification of periostin as a critical marker of progression/reversal of hypertensive nephropathy.

Guerrot et al., *PLoS One*, 2012; 7(3):e31974.

"... the results identify Periostin as a previously unrecognized marker associated with hypertensive nephropathy."

Periostin Induces Kidney Fibrosis after Acute Kidney Injury via the p38 MAPK Pathway.

An et al., *Am J Physiol Renal Physiol*, 2019; 316(3):F426-F437.

"Periostin promotes kidney fibrosis via the p38 MAPK pathway following acute kidney injury triggered by a hypoxic or ischemic insult. Periostin ablation may protect against chronic kidney disease progression."

Periostin as a tissue and urinary biomarker of renal injury in type 2 diabetes mellitus.

Satirapoj et al., *PLoS One*, 2015; 17;

10(4):e0124055.

"Urinary periostin is an associated renal derangement in patients with established diabetic nephropathy and it may be used as an early marker of diabetic renal injury."

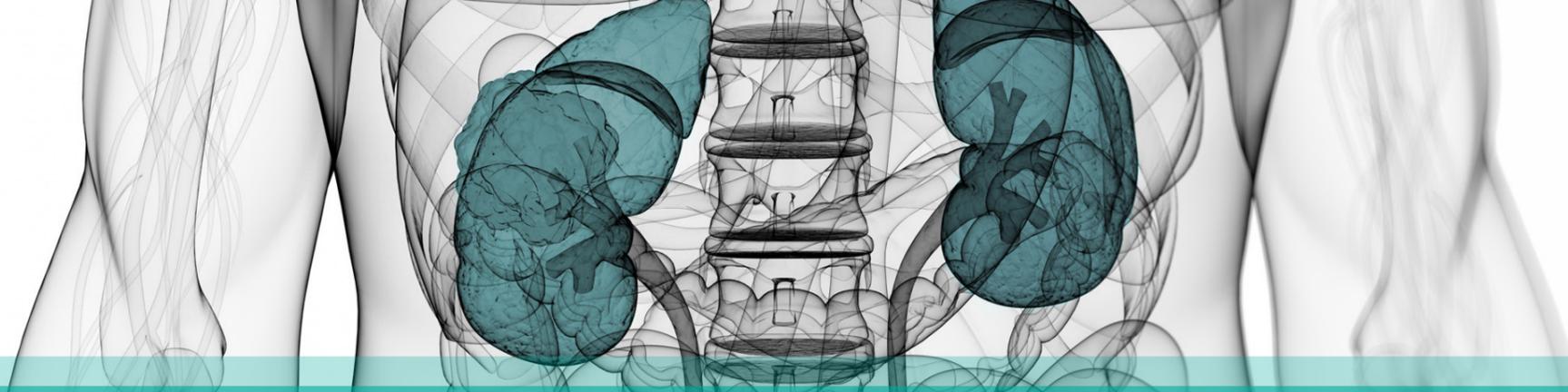
Urinary Periostin Excretion Predicts Renal Outcome in IgA Nephropathy.

Hwang et al., *Am J Nephrol*, 2016;

44(6):481-492.

"POSTN/Cr value at initial diagnosis correlated with renal fibrosis and predicted the renal outcomes in patients with IgAN. It could be a promising urinary biomarker for renal fibrosis."

* measured with Biomedica ELISA



NT-proANP

• NT-proBNP

α-KLOTHO

• ANTI C4d

NT-proANP

PREDICTOR OF PROGRESSION OF KIDNEY DISEASE

Pro-A-type natriuretic peptide and pro-adrenomedullin predict progression of chronic kidney disease: the MMKD Study.

Dieplinger et al., Kidney International, 2009; 75(4):408-414.

"... increased MR-proANP and MR-proADM plasma concentrations at baseline are powerful predictors of progression of kidney disease. Therefore, both markers might be clinically useful as predictors in patients with primary nondiabetic CKD."

Plasma levels of N-terminal proatrial natriuretic peptide in children are dependent on renal function and age.

Holmström et al., Scan J Clin Lab Invest, 2000; 60(2):149-159.

"... plasma levels of Nt-proANP are age-dependent. Moderately elevated values were registered in children with severe renal impairment. Heart failure is regularly associated with excessive elevation of Nt-proANP in plasma. Our findings suggest that the influence of heart failure on levels of this peptide in children greatly exceeds the influence of renal dysfunction."

NT-proBNP

PROGNOSTIC VALUE IN PREDICTING RRT IN STAGE 4 and 5 CKD, PREDICTION OF CV EVENTS AND FOR RISK STRATIFICATION IN HYPERTENSION

Clinical Value of Natriuretic Peptides in Predicting Time to Dialysis in Stage 4 and 5 Chronic Kidney Disease Patients.

Sundqvist et al., PLoS One, 2016; 11(8):e0159914.

"Our results indicate a prognostic value for BNP and NT-proBNP in predicting RRT in stage 4 and 5 CKD patients, regarding both short- and long-term periods. NT-proBNP also proved a value in predicting cardiovascular events. Natriuretic peptides could be useful predictive biomarkers for therapeutic guidance in CKD."

Plasma NT-proBNP mirrors the deleterious cardiovascular and renal continuum in hypertension.

Courand et al., Eur J Prev Cardiol, 2017; 24(5):452-459.

"... NT-proBNP mirrors the harmful effect of high BP on TOD. NT-proBNP could be used as an integrative tool for risk stratification in hypertension."

Cardiac and Stress Biomarkers and Chronic Kidney Disease Progression: The CRIC Study.

Bansal et al., Clin Chem, 2019; pii: clinchem.2019.305797.

"Increases in GDF-15, NT-proBNP, and hsTnT are associated with greater risk for CKD progression. These biomarkers may inform mechanisms underlying kidney injury."

α-KLOTHO

PROGNOSTIC AND DIAGNOSTIC MARKER FOR CHRONIC KIDNEY DISEASE

The Prognostic Role of Klotho in Patients with Chronic Kidney Disease: A Systematic Review and Meta-analysis

Liu et al., Dis Markers, 2019; 2:6468729.

"... sKlotho could be used as a novel biomarker for early diagnosis and prognostic assessment for patients with chronic kidney disease."

Potential application of klotho in human chronic kidney disease.

Neyra et al., Bone, 2017; 100:41-49.

"Klotho is not only a diagnostic and/or prognostic marker for CKD, but the treatment of Klotho deficiency may be a promising strategy to prevent, retard, and decrease the burden of comorbidity in CKD."

Serum levels of soluble secreted α-Klotho are decreased in the early stages of chronic kidney disease, making it a probable novel biomarker for early diagnosis.

Shimamura et al., Clin Exp Nephrol, 2012; 16(5):722-729.

"... soluble α-Klotho may thus represent a new biomarker for the diagnosis of CKD, especially in the early stage."

ANTI C4d

IDENTIFICATION OF ACUTE ANTIBODY-MEDIATED REJECTION IN TRANSPLANTED KIDNEYS

Glomerular C4d deposition can precede the development of focal segmental glomerulosclerosis.

van de Lest et al., Kidney Int, 2019; 96(3):738-749.

"Glomerular C4d deposition can precede the development of FSGS, suggesting that complement activation may play a pathogenic role in the development of FSGS."

The Importance of C4d in Biopsies of Kidney Transplant Recipients.

Corrêa, Clin Develop Immun, 2013; 2013:678180.

"Further studies on AMR with positive C4d staining in biopsy specimens are really important, as well as the study of novel routine markers that may participate in the pathogenesis of this process."

Response to Treatment and Long-Term Outcomes in Kidney Transplant Recipients with Acute T Cell-Mediated Rejection.

Bouatou et al., Am J Transplant, 2019; 19(7):1972-1988.

"Thus, clinical, histological, and immunological assessment of response to treatment of acute TCMR revealed different profiles of the response to treatment with distinct outcomes."

Setting the standard for clinical research.

FGF23 intact ELISA (Cat.No. BI-20700)

Method Sandwich ELISA, 12x8 tests
Sample matrix Plasma (EDTA, heparin, citrate), serum, urine, cell culture supernatant
Sample size 50 µl / well
Standard points 0/50/100/200/400/800/1600 pg/ml
Incubation time 3 h / 30 min

Endostatin ELISA (Cat.No. BI-20742)

Method Sandwich ELISA, 12x8 tests
Sample matrix Plasma (citrate, EDTA, heparin), serum, urine
Sample size 10 µl / sample
Standard points 0/25/50/100/200/400/800 pmol/l
Incubation time 3 h / 1 h / 30 min

Osteoprotegerin ELISA (Cat.No. BI-20403)

Method Sandwich ELISA, 12x8 tests
Sample matrix Serum, plasma (citrate, EDTA, heparin)
Sample size 20 µl / well
Standard points 0/1.25/2.5/5/10/20 pmol/l
Incubation time 4 h / 1 h / 30 min

Sclerostin ELISA (Cat.No. BI-20492)

Method Sandwich ELISA, 12x8 tests
Sample matrix Serum, plasma (EDTA, heparin)
Sample size 20 µl / well
Standard points 0/15/30/60/120/240 pmol/l
Incubation time 20-24 h / 1 h / 30 min

Vanin-1 (Urine) ELISA (Cat.No. BI-VAN1U)

Method Sandwich ELISA, 12x8 tests
Sample matrix Urine
Sample size 10 µl / well
Standard points 0/37.5/75/150/300/600/1200 pmol/l
Incubation time 4 h / 30 min

Angiopietin-2 ELISA (Cat.No. BI-ANG2)

Method Sandwich ELISA, 12x8 tests
Sample matrix Serum, plasma (EDTA, heparin)
Sample size 20 µl / sample
Standard points 0/12.5/25/50/100/200/400 pmol/l
Incubation time 2 h / 1h / 30 min

NT-proANP ELISA (Cat.No. BI-20892)

Method Sandwich ELISA, 12x8 tests
Sample matrix Serum, plasma (EDTA, heparin), cell culture supernatant, urine
Sample size 10 µl / well
Standard points 0/0.63/1.25/2.5/5/10 nmol/l
Incubation time 3h / 30 min

FluoBolt™ KLOTHO (Cat.No. FY-FIA1704)

Method Sandwich Fluorescence IA, 12x8 tests
Sample matrix Serum, plasma
Sample size 10 µl / well
Standard points 0/25/50/100/200/400 pmol/l
Incubation time single step, overnight

FGF23 (C-terminal) ELISA (Cat.No. BI-20702)

Method Sandwich ELISA, 12x8 tests
Sample matrix Serum, plasma (EDTA, heparin, citrate)
Sample size 50 µl / well
Standard points 0/0.2/0.6/1.8/5/10/20 pmol/l
Incubation time 20-24 h / 1 h / 30 min

Endostatin Mouse/Rat ELISA (Cat.No. BI-20742MR)

Method Sandwich ELISA, 12x8 tests
Sample matrix Serum, plasma
Sample size 5 µl / sample
Standard points 0/1/2/4/8/16/32 pmol/l
Incubation time 2 h / 30 min

Big Endothelin ELISA (Cat.No. BI-20082H)

Method Sandwich ELISA, 12x8 tests
Sample matrix Serum, plasma (citrate, EDTA, heparin)
Sample size 50 µl / well
Standard points 0/0.1/0.2/0.4/1/3 pmol/l
Incubation time 4 h / 1 h / 30 min

Bioactive Sclerostin ELISA (Cat.No. BI-20472)

Method Sandwich ELISA, 12x8 tests
Sample matrix Serum, plasma (EDTA, citrate)
Sample size 20 µl / well
Standard points 0/10/20/40/80/160/320 pmol/l
Incubation time 2 h / 1 h / 30 min

Vanin-1 Mouse/Rat ELISA (Cat.No. BI-VAN1MR)

Method Sandwich ELISA, 12x8 tests
Sample matrix Serum, plasma and urine
Sample size 5 µl / sample
Standard points 0/6.25/12.5/25/50/100/200 pmol/l
Incubation time 4 h / 30 min

Angiopietin-2 Mouse/Rat ELISA (Cat.No. BI-ANG2MR)

Method Sandwich ELISA, 12x8 tests
Sample matrix Serum, plasma (EDTA, heparin)
Sample size 5 µl / well
Standard points 0/43.75/87.5/175/350/700/1400 pmol/l
Incubation time 2 h / 2h / 1h / 30 min

NT-proBNP ELISA (Cat.No. SK-1204)

Method Sandwich ELISA, 12x8 tests
Sample matrix Serum, plasma (EDTA)
Sample size 50 µl / well
Standard points 0/10/40/160/640 pmol/l
Incubation time 3h / 30 min

Anti C4d Antibody (Cat. No. BI-RC4D)

Method: Immunohistochemistry, indirect immunofluorescence
Sample type: Paraffin embedded tissue sections, frozen sections