BIOMARKERS IN CLINICAL NEPHROLOGY

Setting the standard for clinical research.
**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.


"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.


"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.


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

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


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

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

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.
“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.
“... 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.
“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.
“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.”

ANGIOPOIETIN-2

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

Angiopoietin-2, Renal Deterioration, Major Adverse Cardiovascular Events and All-Cause Mortality in Patients with Diabetic Nephropathy.
“Angpt2 is an independent predictor of adverse clinical outcomes in diabetic patients.”

Circulating Angiopoietin-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 angiopoietin-2 levels increase with progress of chronic kidney disease.
“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 angiopoietin-2 in adverse renal outcomes of chronic kidney disease.
“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 HFrEF, a single cut-off point of Big-ET-1 was appropriate in the diagnosis of HFrEF, regardless of the presence or absence of CKD. An additional measurement of Big-ET-1 improves the diagnosis of HFrEF 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."

"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**

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

"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."

"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."

"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

PREDICTOR OF PROGRESSION OF KIDNEY DISEASE


“... 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


“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.”


“... 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.”


“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.
“... 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.
vande 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.
“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.
“Thus, clinical, histological, and immunological assessment of response to treatment of acute TCMR revealed different profiles of the response to treatment with distinct outcomes.”
<table>
<thead>
<tr>
<th>ELISA Test</th>
<th>Method</th>
<th>Sample Matrix</th>
<th>Sample Size</th>
<th>Standard Points</th>
<th>Incubation Time</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FGF23 intact ELISA</strong> (Cat.No. BI-20700) – C⃝</td>
<td>Sandwich ELISA, 12x8 tests</td>
<td>Plasma (EDTA, heparin, citrate), serum, urine, cell culture supernatent</td>
<td>50 μl / well</td>
<td>0/50/100/200/400/800/1600 pg/ml</td>
<td>3 h / 30 min</td>
</tr>
<tr>
<td><strong>FGF23 (C-terminal) ELISA</strong> (Cat.No. BI-20702) – C⃝</td>
<td>Sandwich ELISA, 12x8 tests</td>
<td>Serum, plasma (EDTA, heparin, citrate)</td>
<td>50 μl / well</td>
<td>0/0.2/0.6/1.8/5/10/20 pmol/l</td>
<td>20-24 h / 1 h / 30 min</td>
</tr>
<tr>
<td><strong>Endostatin ELISA</strong> (Cat.No. BI-20742)</td>
<td>Sandwich ELISA, 12x8 tests</td>
<td>Plasma (citrate, EDTA, heparin), serum, urine</td>
<td>10 μl / sample</td>
<td>0/25/50/100/200/400/800 pmol/l</td>
<td>3 h / 1 h / 30 min</td>
</tr>
<tr>
<td><strong>Endostatin Mouse/Rat ELISA</strong> (Cat.No. BI-20742MR)</td>
<td>Sandwich ELISA, 12x8 tests</td>
<td>Serum, plasma</td>
<td>5 μl / sample</td>
<td>0/1/2/4/8/16/32 pmol/l</td>
<td>2 h / 30 min</td>
</tr>
<tr>
<td><strong>Osteoprotegerin ELISA</strong> (Cat.No. BI-20403) – C⃝</td>
<td>Sandwich ELISA, 12x8 tests</td>
<td>Serum, plasma (citrate, EDTA, heparin)</td>
<td>20 μl / well</td>
<td>0/1.25/2.5/5/10/20 pmol/l</td>
<td>4 h / 1 h / 30 min</td>
</tr>
<tr>
<td><strong>Big Endothelin ELISA</strong> (Cat.No. BI-20082H) – C⃝</td>
<td>Sandwich ELISA, 12x8 tests</td>
<td>Serum, plasma (EDTA, citrate)</td>
<td>20 μl / well</td>
<td>0/0.1/0.2/0.4/1/3 pmol/l</td>
<td>4 h / 1 h / 30 min</td>
</tr>
<tr>
<td><strong>Sclerostin ELISA</strong> (Cat.No. BI-20492)</td>
<td>Sandwich ELISA, 12x8 tests</td>
<td>Serum, plasma (citrate, EDTA, heparin)</td>
<td>50 μl / well</td>
<td>0/0.1/0.2/0.4/1/3 pmol/l</td>
<td>4 h / 1 h / 30 min</td>
</tr>
<tr>
<td><strong>Bioactive Sclerostin ELISA</strong> (Cat.No. BI-20472)</td>
<td>Sandwich ELISA, 12x8 tests</td>
<td>Serum, plasma (EDTA, citrate)</td>
<td>20 μl / well</td>
<td>0/10/20/40/80/160/320 pmol/l</td>
<td>2 h / 1 h / 30 min</td>
</tr>
<tr>
<td><strong>Vanin-1 (Urine) ELISA</strong> (Cat.No. BI-VAN1U)</td>
<td>Sandwich ELISA, 12x8 tests</td>
<td>Urine</td>
<td>10 μl / well</td>
<td>0/37.5/75/150/300/600/1200 pmol/l</td>
<td>4 h / 30 min</td>
</tr>
<tr>
<td><strong>Vanin-1 Mouse/Rat ELISA</strong> (Cat.No. BI-VAN1MR)</td>
<td>Sandwich ELISA, 12x8 tests</td>
<td>Serum, plasma and urine</td>
<td>5 μl / sample</td>
<td>0/6.25/12.5/25/50/100/200 pmol/l</td>
<td>4 h / 30 min</td>
</tr>
<tr>
<td><strong>Angiopoietin-2 ELISA</strong> (Cat.No. BI-ANG2)</td>
<td>Sandwich ELISA, 12x8 tests</td>
<td>Serum, plasma (EDTA, heparin)</td>
<td>5 μl / sample</td>
<td>0/43.75/87.5/175/350/700/1400 pmol/l</td>
<td>2 h / 2h / 1h / 30 min</td>
</tr>
<tr>
<td><strong>Angiopoietin-2 Mouse/Rat ELISA</strong> (Cat.No. BI-ANG2MR)</td>
<td>Sandwich ELISA, 12x8 tests</td>
<td>Serum, plasma (EDTA, heparin)</td>
<td>5 μl / sample</td>
<td>0/43.75/87.5/175/350/700/1400 pmol/l</td>
<td>2 h / 2h / 1h / 30 min</td>
</tr>
<tr>
<td><strong>NT-proANP ELISA</strong> (Cat.No. BI-20892) – C⃝</td>
<td>Sandwich ELISA, 12x8 tests</td>
<td>Serum, plasma (EDTA, heparin), cell culture supernatant, urine</td>
<td>10 μl / well</td>
<td>0/0.63/1.25/2.5/5/10 nmol/l</td>
<td>3h / 30 min</td>
</tr>
<tr>
<td><strong>NT-proBNP ELISA</strong> (Cat.No. SK-1204) – C⃝</td>
<td>Sandwich ELISA, 12x8 tests</td>
<td>Serum, plasma (EDTA)</td>
<td>50 μl / well</td>
<td>0/10/40/160/640 pmol/l</td>
<td>3h / 30 min</td>
</tr>
<tr>
<td><strong>Anti C4d Antibody</strong> (Cat. No. BI-RC4D) – C⃝</td>
<td>Immunohistochemistry, indirect immunofluorescence</td>
<td>Paraffin embedded tissue sections, frozen sections</td>
<td>10 μl / well</td>
<td>0/25/50/100/200/400 pmol/l</td>
<td>single step, overnight</td>
</tr>
</tbody>
</table>