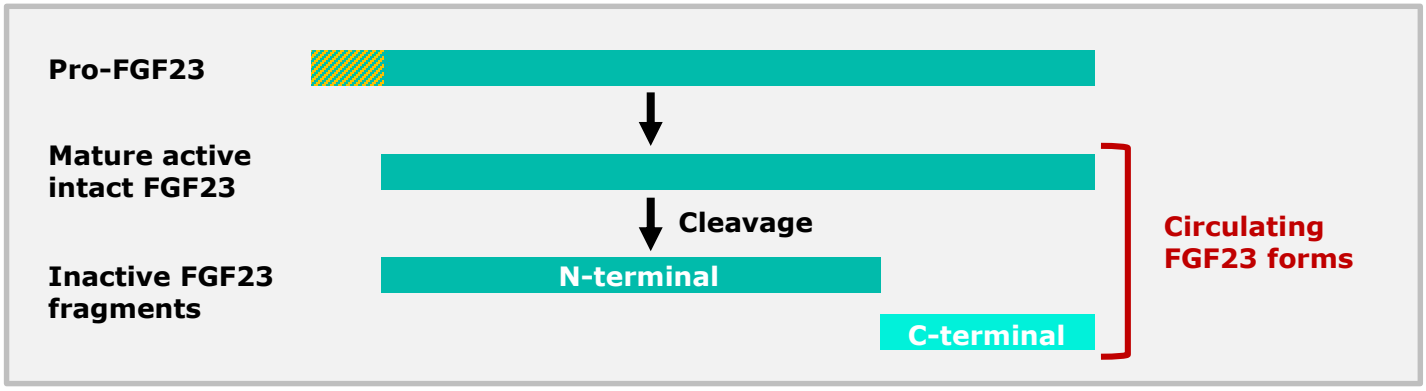
FGF23 – An Overview

FGF23 Production

FGF23 is an endocrine hormone regulating phosphate homeostasis by modulating renal phosphate reabsorption, vitamin D metabolism and parathyroid hormone (PTH) secretion.
Epidemiological data suggest that higher FGF23 concentrations are associated with all-cause mortality, cardiovascular mortality, a higher risk of myocardial infarction, stroke and heart failure.

FGF23 (fibroblast growth factor 23) is a member of the fibroblast growth factor family and controls phosphate and vitamin D homeostasis. The full-length protein comprises 251 amino acids including a 24 amino acid signal peptide. The N-terminal FGF homology region of FGF23 is separated from the unique C-terminal region by a proteolytic cleavage site. A proportion of FG23 is proteolytically processed between arginine179 and serine180 to generate N-terminal and C-terminal fragments. Therefore, the major forms of FGF23 present in human circulation are hormonally intact FGF23 and inactive N-terminal and C-terminal fragments.
FGF23 binds to FGF receptor 1c (FGFR1c) with its N-terminal region, while the C-terminal region is capable of interacting with the co-receptor αKlotho to confer high-affinity binding to the receptor. FGFR1c and αKlotho are expressed in the distal nephron and the parathyroid gland. Co-receptor independent signaling of FGF23 has been described for other FGFRs, which are expressed in a variety of tissues. The main source of FGF23 are osteocytes in the bone.



FGF23 Assays

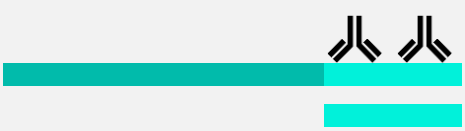
The FGF23 (intact) human ELISA is a sandwich-based immunoassay with an anti-human FGF23 capture antibody recognizing a structural epitope in the N-terminal part of FGF23 and a detection antibody binding to the C-terminal part of mature FGF23.

By contrast, the FGF23 (C-terminal) multi-matrix ELISA is a sandwich-based immunoassay, which recognizes multiple epitopes in the C-terminal part of FGF23.

FGF23 (intact) human ELISA

- Catalogue number: BI-20700
- Specificity: Intact FGF23
- Sample types: Preferable plasma, serum possible
- Sample volume: 50 µl / test
- Assay time: 3.5 h
- Sensitivity: 5.4 pg/ml
- Standard range: 0 to 1600 pg/ml
- **Use: CE-marked**

FGF23 (C-terminal) multi-matrix ELISA



- Catalogue number: BI-20702
- Specificity: Intact FGF23 & C-terminal fragments
- Sample types: Plasma & serum
- Sample volume: 50 µl / test
- Assay time: Overnight
- Sensitivity: 0.6 pg/ml
- Standard range: 0 to 150.4 pg/ml
- **Use: CE-marked**

FGF23 as a predictor of cardiovascular events in community-based cohorts

Main Findings / Conclusion	Target Population / Study Design	Analyte	First Author and Reference
Elevated serum FGF23 levels, even within the normal range, are associated with increased LVMI and increased risk for the presence of LVH in elderly subjects.	PIVUS: community-based cohort n = 795	intact FGF23	*Mirza MA et al., Atherosclerosis. 2009; 207(2):546-51.*
Elevated serum FGF23 concentrations are independently associated with prevalent cardiovascular disease in older community-dwelling women.	Community-dwelling women (aged 70–79 years) n = 659	intact FGF23	*Dalal M et al., Eur J Endocrinol. 2011; 165(5):797-803.*
FGF23 is a predictor of cardiovascular events in the community, and its predictive value is independent of confounders of mineral metabolism and measurements portraying multiple dimensions of cardiovascular pathology.	PIVUS: community-based prospective investigation of the vasculature in seniors (mean age 70 years) n = 973	intact FGF23	*Ärnlöv J et al., Clin J Am Soc Nephrol. 2013; 8(5): 781-6.*
Higher serum FGF23 was associated with a significantly increased risk for cardiovascular mortality.	ULSAM: longitudinal study-adult men population-based cohort (mean age 77 years, median follow-up 9.7 years) n = 727 men	intact FGF23	*Ärnlöv J et al., Kidney Int. 2013; 83(1):160-6.*
No correlation of FGF23 and CV disease! The mortality rate due to CVD was only 37% of total mortality rate, which may explain the negative result between FGF23 and all-cause mortality.	Population-based cohort (men aged 69–81 years) n = 3,014	intact FGF23	*Westerberg PA et al., BMC Nephrol. 2013; 14:85.*
FGF-23 is independently associated with all cause death and incident HF in community-living older persons. These associations appear stronger in persons with CKD.	Community-living persons (65 years of age. 10 year follow-up) n = 310	C-terminal FGF23	*Ix JH et al., J Am Coll Cardiol. 2012; 60(3):200–207.*
Plasma FGF23 is not associated with the development of incident CHD (coronary heart disease) in men without chronic kidney disease.	Health professionals without kidney disease (10 year follow up) n = 1,259	C-terminal FGF23	*Taylor EN et al., Am Heart J. 2011; 161(5): 956–962.*
Elevated FGF23 was independently associated with increased risk of vascular and nonvascular mortality in a diverse general population and with increased risk of cancer death specifically in Hispanic individuals.	NOMAS: population based prospective cohort (ethnically diverse urban population; age >39, no reported history of stroke. Median follow-up 14 years) n= 2,525	C-terminal FGF23	*Souma N et al., J Clin Endocrinol Metab. 2016;101(10): 3779-3786.*

FGF23 as a predictor of cardiovascular events in patients with heart disease

Main Findings / Conclusion	Target Population / Study Design	Analyte	First Author and Reference
FGF23 was positively associated with LV mass, LV hypertrophy, reduced LV systolic function, and plasma BNP concentration.	Cardiology inpatients (high-risk population for cardiac abnormalities) n = 100	intact FGF23	*Shibata K et al., PLoS One. 2013; 8(9).*
An association between FGF23 and cardiac hypertrophy and systolic dysfunction was observed among patients without CKD as well as those with CKD after multivariate adjustment.	Patients admitted to the cardiology department n = 903	intact FGF23	*Tanaka S et al., PLoS One. 2016; 11(7): e0156860.*
In patients undergoing coronary angiography baseline c-term FGF23 levels predict the risk for all-cause and cardiovascular mortality over 9.9 years of follow-up. These associations were independent of established cardiovascular risk factors and serum phosphate.	LURIC: patients with heart disease (9.9 years follow-up) n = 2,974	C-terminal FGF23	*Brandenburg VM et al., Atherosclerosis. 2014; 237(1):53-9.*
In outpatients patients with stable CAD, higher FGF23 are independently associated with mortality and CVD events. "Compared with participants with FGF-23 levels in the lowest tertile, those in the highest tertile had 2-fold greater risk for mortality after adjustment for traditional CVD risk factors, C-reactive protein levels, and kidney function."	Heart and Soul Study: outpatients with stable coronary artery disease (CAD), median follow-up of 6.0 years n = 833	C-terminal FGF23	*Parker BD et al., Ann Intern Med. 2010; 18; 152(10):640-8.*
-FGF23 independent predictor associated with CV death and incident HF in patients with SIHD (stable ischemic heart disease) -FGF23 predicts response to therapies aimed to reduce HF -Identification of patients with HFREF -Estimation of future CV risk and help to predict the response to ACE therapy in SIHD patients.	PEACE (Prevention of Events With Angiotensin-Converting Enzyme) trial: Patients with SIHD randomly assigned to trandolapril or placebo, followed up for a median of 5.1 years n = 3,627	C-terminal FGF23	*Udell JA et al., J Am Coll Cardiol. 2014; 10;63(22):2421-8.*

FGF23 Ratios And Disease

Circulating levels of FGF23 can be altered in both genetic and acquired diseases. A primary excess in circulating intact FGF23 is the underlying cause of diseases like X-linked hypophosphatemic rickets (XLH), autosomal dominant/recessive hypophosphatemic rickets (ADHR/ARHR) or tumor-induced osteomalacia. The excessive FGF23 levels in these diseases cause renal phosphate wasting, low active vitamin D concentrations and defective mineralization of bones.

Circulating FGF23 is also elevated in patients with chronic kidney disease (CKD), presumably in response to decreased renal excretion of phosphate. During the course of the disease, FGF23 secretion is upregulated and the ratio between C-terminal and intact FGF23 is shifted towards the intact protein.

By contrast, during iron deficiency FGF23 synthesis and cleavage are upregulated in a coupled manner, resulting in low normal levels of intact FGF23 and high levels of cFGF23.

Therefore, different conditions result in varying characteristic iFGF23:cFGF23 ratios. Thus, simultaneous determination of intact and C-terminal FGF23 allows for assessing the production and cleavage of the molecule in different clinical settings. Some examples of this are shown below.