論　文　内　容　要　旨

Effect of FGF23 in maintenance hemodialysis patients
（維持透析患者における FGF23 の影響）

① Addition of novel biomarkers for predicting all-cause and cardiovascular mortality in prevalent hemodialysis patients
（維持透析患者の新規バイオマーカー追加での全死亡死、心血管死予測）
Therapeutic Apheresis and Dialysis, 2017, in press.

② Oral iron supplementation with sodium ferrous citrate reduces the serum intact and c-terminal FGF23 levels of maintenance hemodialysis patients
（クエン酸第一鉄ナトリウムによる経口鉄補充は維持透析患者の iFGF23 と cFGF23 を低下させる）
Nephrology, in press.

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Background/Aim There is a pervasive view that elevated serum fibroblast growth factor 23 (FGF23) levels are responsible for cardiovascular disease and death in maintenance hemodialysis (MHD) patients. Although numerous previous studies have explored various novel biomarkers including FGF23 for predicting mortality in MHD patients, but the majority of these studies were conducted in the United States or Europe. The mortality rates of MHD patients differ greatly among the United States, Europe, and Japan. Based on these findings, the best biomarkers for predicting mortality in Japanese MHD patients might differ from those for American and European MHD patients. Recently, an animal study suggested that iron deficiency stimulates FGF23 transcription in osteocytes. Furthermore, it was reported that the short-term use of iron-based phosphate binders, such as ferric citrate and sucroferric oxyhydroxide, replenished the iron stores and reduced the serum phosphate and FGF23 levels of patients with CKD and HD patients with iron deficiency. Both ferric citrate and sucroferric oxyhydroxide contain ferric iron (Fe^{3+}), whereas sodium ferrous citrate contains ferrous iron (Fe^{2+}). The purpose of this study was to whether the addition of 5 biomarkers [serum N-terminal pro-brain natriuretic peptide (NT-proBNP), intact fibroblast growth factor-23 (FGF23), ß2-microglobulin (ß2MG), cystatin C, and high-sensitivity C-reactive protein (hsCRP)] could improve the prediction of 2-year all-cause and/or cardiovascular mortality in MHD patients. Furthermore, to whether oral ferrous iron (Fe^{2+}) supplementation with sodium ferrous citrate reduces the serum FGF23 levels of MHD patients with iron deficiency in the same way as oral ferric iron (Fe^{3+}).

Methods The subjects of this study were 307 MHD patients who were treated at Ichiyokai Harada Hospital. The patients' serum NT-proBNP, hsCRP, FGF23, cystatin C, ß2MG, Kt/Vurea, hemoglobin, serum albumin, phosphate, intact parathyroid hormone (iPTH), and albumin-adjusted serum calcium (Ca) levels were assessed in Sept 2012. All blood samples were drawn before the beginning and at the end (only for Kt/Vurea) of the first week's hemodialysis session. 24-hour urine samples were obtained from the patients that produced≥100 ml/day urine. The urinary volume was considered to be zero in patients that produced <100 ml/day urine. Next study was a prospective, open-label interventional study, in which eligible patients were given 1 sodium ferrous citrate tablet containing 50 mg of iron a day for 3 months. The subjects of this study were thirty-one MHD patients with iron deficiency who had taken iron supplements during the 8 weeks before the study were excluded. All blood samples were collected before the beginning of the first session of the week both at the baseline (0 months) and after 3 months' treatment with sodium ferrous citrate. The examined outcomes, all of which were assessed at the baseline and after 3 months' sodium ferrous citrate treatment, included the patients' serum transferrin saturation (TSAT), geriatric nutritional risk index (GNRI), erythropoiesis-stimulating agent

resistance (ESA) index, Kt/Vurea, and normalized protein equivalent of nitrogen appearance (nPNA) values, hemoglobin levels, random plasma glucose levels, serum iron, ferritin, intact FGF23 (iFGF23), C-terminal FGF23 (cFGF23), phosphate, magnesium, iPTH, CRP, albumin, and Ca levels.

Result There were 66 all-cause death, and 25 cardiovascular (CV) deaths during two years and assessed using Cox models and concordance (C)-statistics. The addition of NT-proBNP alone ($P<0.05$) or NT-proBNP, hsCRP, and β2MG as a panel (C-statistics: 0.834 vs. 0.776, $P<0.01$) to a conventional risk model composed of age, diabetes, and the serum albumin level significantly improved the prediction of 2-year all-cause mortality, and the addition of NT-proBNP and hsCRP as a panel to a conventional risk model composed of age significantly improved the prediction of 2-year CV mortality ($P<0.05$) in MHD patients. Neither FGF23 nor cystatin C improved mortality prediction. Next study, compared with their baseline (0 months) values, the patients' serum iron, TSAT values and ferritin levels were significantly increased after 3 months' sodium ferrous citrate supplementation. Both the patients' serum iFGF23 and cFGF23 levels were significantly reduced after 3 months' sodium ferrous citrate supplementation, but their iFGF23: cFGF23 ratios were not significantly altered. While their serum hemoglobin levels were not significantly altered after 3 months' treatment, their ESA index values were significantly reduced. The patients' serum CRP levels were significantly reduced after 3 months' treatment. Conversely, their serum albumin and GNRI values were significantly increased after 3 months' treatment. No significant changes in the patients' serum phosphate, Ca, magnesium, or iPTH levels, random plasma glucose levels, or Kt/Vurea or nPNA values were seen after 3 months' oral sodium ferrous citrate treatment.

Conclusion The addition of novel biomarkers, i.e., NT-proBNP alone or NT-proBNP, hsCRP, and β2MG as a panel, to a conventional risk model (age, presence of diabetes, serum albumin) significantly improved the prediction of 2-year all-cause mortality, and the addition of novel biomarkers, i.e., NT-proBNP and hsCRP as a panel, to a conventional risk model (age) significantly improved the prediction of 2-year CV mortality in MHD patients. Short-term oral iron supplementation with sodium ferrous citrate replenished the iron stores and reduced the serum iFGF23 and cFGF23 levels of MHD patients with iron deficiency without affecting their serum phosphate, Ca, or iPTH levels.