***Discussion***

**Vitamin D deficiency and vascular calcification**

Female gender had been shown to be associated with 25-hydroxyvitamin D (25D) deficiency in hemodialysis patients (1,2). However, the relationship between the serum vitamin D level and vascular calcification scores in hemodialysis patients remained unclear. Chang et al. illustrated a negative correlation of 25D levels with the Kauppila index in 289 hemodialysis patients from a cohort in South Korea (2). Wang et al. revealed a similar result, where 25D levels were negatively related to the Kauppila index in 126 hemodialysis patients from China (3). In both studies, 25D levels lost their significances after adjustment. Kanbay et al. studied 177 patients with CKD stages 2 to 3 (eGFR 30–90 mL/min/1.73m2), in which 25D levels showed no significant correlation with Gensini score in univariate analysis (4). The relationship between 25D and vascular calcification in different genders remained unclear, but the evidences may support some level of association between female gender and vascular calcification.

**Parathyroid hormone, sclerostin, FGF-23 and vascular calcification**

Parathyroid hormones had been shown to induce phosphaturic response, decrease reabsorption of calcium and phosphate from urine and increase uptake of calcium and phosphate from intestines and bone into the bloodstream. Patients with higher PTH showed increased risk of low bone mass, Kirkpantur et al. inferred a negative relation between serum PTH level and bone mineral densities, with a standard regression coefficient of -0.21– -0.33 (5). Intact PTH is shown to be related with Gensini vascular calcification score, with a correlation coefficient of 0.152, p = 0.044 (4). However, PTH levels showed no relation with vascular calcification when the calcification was assessed with SVCS in an Egypt cohort of 73 patients with CKD stages 5 to 5T (6). In a Belgium cohort with 268 kidney transplant patients, lower PTH was identified as an independent determinant of higher serum sclerostin levels, which was related to lower baseline aortic calcification score (7). Moreover sclerostin was suggested to play a role in reducing mineralization during the late phase of vascular calcification in hemodialysis patients (8). Interestingly, a very low parathyroid hormone (PTH) level (VLPL) serves as a risk of bone disease, vascular calcification, and mortality in hemodialysis patients (9). FGF-23 serves as a risk factor for an increase in Gensini score (R = 0.868; P = 0.001) in a cohort with 177 patients ranging from CKD stage 2 to 4 (4). Turan et al. also confirmed, although small, the risk for CACS per 50 pg/mL increase of FGF-23 in 224 hemodialysis patients (10). Tamei et al. conducted a study including 127 hemodialysis patients and inferred that FGF-23 serves as a significant modifier for aortic artery calcification score over progression 5 year of follow-up (11). Moreover, patients with abdominal aortic calcification of Kauppila index > 5 are prone to have impaired FGF23-induced phosphaturic response, whereas the impairment of PTH-induced phosphaturia was not discovered (12). Claes et al. conducted a study including 193 kidney transplant patients in Belgium and showed that PTH levels were independently associated with the prolongation of the corrected duration of QT interval (13).

**Age and vascular calcification**

Older age had been shown to associate with higher vascular calcification risk in CKD patients (6,12,14–17), but a study by Jung et al. on 40 hemodialysis patients in South Korea showed that age only serves as a modifier for annualized change of CAC score in male patients (R = 0.500, p = 0.009), but the same trend was not discovered in female gender (18). A France study including 24 hemodialysis patients also confirmed the exclusive relation between age and calcification in male (19). Also, an increase in age was associated with higher levels of serum sclerostin (7), suggesting sclerostin may not be a major influencer in the observed tendency of vascular calcification in older patients.

1. Jean G, Charra B, Chazot C. Vitamin D Deficiency and Associated Factors in Hemodialysis Patients. J Ren Nutr. 2008;18(5):395–9.

2. Chang JH, Ro H, Kim S, Lee HH, Chung W, Jung JY. Study on the relationship between serum 25-hydroxyvitamin D levels and vascular calcification in hemodialysis patients with consideration of seasonal variation in vitamin D levels. Atherosclerosis. 2012;220(2):563–8.

3. Wang F, Wu S, Ruan Y, Wang L. Correlation of serum 25-hydroxyvitamin D level with vascular calcification in hemodialysis patients. Int J Clin Exp Med. 2015;8(9):15745–51.

4. Kanbay M, Nicoleta M, Selcoki Y, Ikizek M, Aydin M, Eryonucu B, et al. Fibroblast growth factor 23 and fetuin A are independent predictors for the coronary artery disease extent in mild chronic kidney disease. Clin J Am Soc Nephrol. 2010;5(10):1780–6.

5. Kirkpantur A, Altun B, Hazirolan T, Akata D, Arici M, Kirazli S, et al. Association Among Serum Fetuin-A Level, Coronary Artery Calcification, and Bone Mineral Densitometry in Maintenance Hemodialysis Patients. Artif Organs. 2009;33(10):844–54.

6. Maharem DA, Gomaa SH, El Ghandor MK, Mohamed EI, Matrawy KA, Zaytoun SS, et al. Association of serum fetuin-A and fetuin-A gene polymorphism in relation to mineral and bone disorders in patients with chronic kidney disease. Egypt J Med Hum Genet. 2013;14(4):337–52.

7. Evenepoel P, Goffin E, Meijers B, Kanaan N, Bammens B, Coche E, et al. Sclerostin serum levels and vascular calcification progression in prevalent renal transplant recipients. J Clin Endocrinol Metab. 2015;100(12):4669–76.

8. Viaene L, Behets GJ, Claes K, Meijers B, Blocki F, Brandenburg V, et al. Sclerostin: another bone-related protein related to all-cause mortality in haemodialysis? Nephrol Dial Transplant. 2013;28(12):3024–30.

9. Jean G, Lataillade D, Genet L, Legrand E, Kuentz F, Moreau-Gaudry X, et al. Association between Very Low PTH Levels and Poor Survival Rates in Haemodialysis Patients: Results from the French ARNOS Cohort. NEPHRON Clin Pract. 2011;118(2):c211–6.

10. Turan MN, Kircelli F, Yaprak M, Sisman AR, Gungor O, Bayraktaroglu S, et al. FGF-23 levels are associated with vascular calcification, but not with atherosclerosis, in hemodialysis patients. Int Urol Nephrol. 2016;48(4):609–17.

11. Tamei N, Ogawa T, Ishida H, Ando Y, Nitta K. Serum Fibroblast Growth Factor-23 Levels and Progression of Aortic Arch Calcification in Non-Diabetic Patients on Chronic Hemodialysis. J Atheroscler Thromb. 2011;18(3):217–23.

12. Craver L, Dusso A, Martinez-Alonso M, Sarro F, Valdivielso JM, Fernandez E. A low fractional excretion of Phosphate/Fgf23 ratio is associated with severe abdominal Aortic calcification in stage 3 and 4 kidney disease patients. BMC Nephrol. 2013;14.

13. Qureshi AR, Olauson H, Witasp A, Haarhaus M, Brandenburg V, Wernerson A, et al. Increased circulating sclerostin levels in end-stage renal disease predict biopsy-verified vascular medial calcification and coronary artery calcification. KIDNEY Int. 2015;88(6):1356–64.

14. Chiu Y-W, Adler SG, Budoff MJ, Takasu J, Ashai J, Mehrotra R, et al. Coronary artery calcification and mortality in diabetic patients with proteinuria. Kidney Int. 2010;77(12):1107–14.

15. Gelev S, Spasovski G, Trajkovski Z, Damjanovski G, Amitov V, Selim G, et al. Factors associated with various arterial calcifications in haemodialysis patients. Prilozi. 2008;29(2):185–99.

16. Chen Z, Qureshi AR, Parini P, Hurt-Camejo E, Ripsweden J, Brismar TB, et al. Does statins promote vascular calcification in chronic kidney disease? Eur J Clin Invest. 2017;47(2):137–48.

17. Golembiewska E, Qureshi AR, Dai L, Lindholm B, Heimbürger O, Söderberg M, et al. Copeptin is independently associated with vascular calcification in chronic kidney disease stage 5. BMC Nephrol. 2020 Feb 7;21(1):43.

18. Jung HH, Kim S-W, Han H. Inflammation, mineral metabolism and progressive coronary artery calcification in patients on haemodialysis. Nephrol Dial Transplant. 2006;21(7):1915–20.

19. Oprisiu R, Bunea D, Tarek S, Hedi B, Fournier A. Progression of vascular calcification and dyslipidemia in patients on chronic hemodialysis. Vol. 39, American Journal of Kidney Diseases. 2002. p. 209.