EDITORIAL

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A biomarker, osteoprotegerin, in patients undergoing hemodialysis

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Despite progress in patient care and increased understanding of the pathophysiology, high morbidity and mortality rates have persisted in patients with end-stage renal disease (ESRD). This is primarily due to the high incidence of cardiovascular events in patients with ESRD, and many attempts have been made to try to increase survival and improve the quality of life of patients undergoing dialysis. Because of the severity of cardiovascular disease (CVD), which could manifest as sudden death, and the associated pathologies, efforts for disease prevention in high-risk populations are likely to be the most effective treatment strategy. However, in addition to traditional cardiovascular risk factors such as hypertension, hyperlipidemia, diabetes mellitus, and obesity, nontraditional risk factors such as inflammation, malnutrition, and chronic kidney disease-mineral bone disorder (CKD-MBD) also to contribute to CVD in patients undergoing dialysis. It is therefore challenging to identify high-risk patients. The measurement of vascular calcification and arterial stiffness is one way to identify patients susceptible to CVD. Several methods are used to quantify these parameters, including radiologic examinations such as plain radiography and computed tomography, or the measurement of pulse wave velocity. Although some studies demonstrated the usefulness of these traditional methods for identifying individuals at risk of developing CVD, they are not considered sufficient to accurately estimate risk, due to their relatively low sensitivity and specificity.

The measurement of biomarker in blood related to atherosclerosis or vascular calcification to predict cardiovascular events has gained interest for reasons of convenience. However, this only has real diagnostic value if the biomarkers are accurately validated. The identification of biomarkers could also provide insight into disease pathogenesis, which is fundamental for the development of targeted therapies. In addition to C-reactive protein and low density lipoprotein cholesterol, which are accepted as cardiovascular risk factors, other markers, including natriuretic peptide, apolipoprotein, homocysteine, and troponin I, are correlated with cardiovascular events in the general population. However, due to the complexity of the pathophysiology of CVD in patients undergoing dialysis, none of these have been accepted as useful biomarkers to predict CVD in these individuals.

Osteoprotegerin (OPG) is a cytokine

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that belongs to the tumor necrosis factor receptor superfamily. It is produced by osteoblasts, endothelial cells, and vascular smooth muscle cells [1]. OPG interferes with binding of the receptor activator for nuclear factor-κB ligand (RANKL) to its cell surface receptor by functioning as a decoy receptor, thus inhibiting the differentiation and activity of osteoclasts [2]. In bone, OPG has an antiosteoclastic effect because it regulates bone resorption [3]. Although the actions of OPG in the vasculature and heart are not fully understood, increased expression of OPG and RANKL occur in atherosclerotic lesions, which promotes vascular calcification [4]. As reported by Lee et al. [5] in the current issue, recent epidemiological studies have suggested a predictive role of serum OPG in coronary calcification and cardiovascular mortality, both in predialysis patients, and in patients treated with hemodialysis and peritoneal dialysis [6-10]. Most studies suggested that higher OPG levels were associated with advanced vascular calcification and arterial stiffness. In addition to its role in vascular calcification, OPG contributes to the development of CVD by modulating inflammation and endothelial dysfunction [6]. However, the exact role of OPG in atherosclerosis remains unclear. Interestingly, OPG-deficient mice displayed calcified arterioles [11], and treatment with OPG attenuated aortic valve calcification [12]. The detailed mechanism for these effects is yet to be elucidated, and should be studied further.

Given that OPG originates in bone, it may link CKD-MBD with the progression of CVD. Recent studies revealed that serum OPG levels increased concurrently with CKD progression, which was positively correlated with fibroblast growth factor-23 [8], but negatively correlated with bone mineral density (BMD) [13]. This suggests a potential role for OPG in CKD-MBD. Because OPG would be expected to exert a protective effect on BMD, it is likely that the increase in circulating OPG is a compensatory response. However, the interaction between OPG and additional factors in bone metabolism requires further investigation.

Although it would be premature to conclude that OPG is a reliable early biomarker for the prediction of cardiovascular events in dialysis patients, it may be useful to classify at risk patients, particularly when combined with an additional modality for risk stratification. For OPG to be validated as a biomarker, future studies should apply prospective screening to a large cohort of patients. In addition, OPG could be tested in randomized controlled trials to assess whether it has therapeutic potential. Moreover, studies should be conducted to identify confirmatory diagnostic protocols for detecting cardiovascular events as early as possible. This will also help bring new developments to the care of patients undergoing dialysis.

Conflict of interest

No potential conflict of interest relevant to this article is reported.

REFERENCES

1. Aoki A, Murata M, Asano T, et al. Association of serum osteoprotegerin with vascular calcification in patients with type 2 diabetes. Cardiovasc Diabetol 2013;12:11.
2. Kiechl S, Werner P, Knoflach M, Furtner M, Willeit J, Schett G. The osteoprotegerin/RANK/RANKL system: a bone key to vascular disease. Expert Rev Cardiovasc Ther 2006;4:801-811.
3. Montagnana M, Lippi G, Danese E, Guidi GC. The role of osteoprotegerin in cardiovascular disease. Ann Med 2013;45:254-264.
4. Hsu H, Lacey DL, Dunstan CR, et al. Tumor necrosis factor receptor family member RANK mediates osteoclast differentiation and activation induced by osteoprotegerin ligand. Proc Natl Acad Sci U S A 1999;96:3540-3545.
5. Lee JE, Kim HJ, Moon SJ, et al. Serum osteoprotegerin is associated with vascular stiffness and the onset of new cardiovascular events in hemodialysis patients. Korean J Intern Med 2013;28:668-677.
6. Lieb W, Gona P, Larson MG, et al. Biomarkers of the osteoprotegerin pathway: clinical correlates, subclinical disease, incident cardiovascular disease, and mortality. Arterioscler Thromb Vasc Biol 2010;30:1849-1854.
7. Pateinakis P, Papagianni A, Douma S, Efstratiadis G, Memmos D. Associations of fetuin-A and osteoprotegerin with arterial stiffness and early atherosclerosis in chronic hemodialysis patients. BMC Nephrol 2013;14:122.

8. Ford ML, Smith ER, Tomlinson LA, Chatterjee PK, Rajkumar C, Holt SG. FGF-23 and osteoprotegerin are independently associated with myocardial damage in chronic kidney disease stages 3 and 4: another link between chronic kidney disease-mineral bone disorder and the heart. Nephrol Dial Transplant 2012;27:727-733.
9. Morena M, Terrier N, Jaussent I, et al. Plasma osteoprotegerin is associated with mortality in hemodialysis patients. J Am Soc Nephrol 2006;17:262-270.
10. Janda K, Krzanowski M, Chowaniec E, et al. Osteoprotegerin as a marker of cardiovascular risk in patients on peritoneal dialysis. Pol Arch Med Wewn 2013;123:149-155.
11. Bennett BJ, Scatena M, Kirk EA, et al. Osteoprotegerin inactivation accelerates advanced atherosclerotic lesion progression and calcification in older ApoE-/- mice. Arterioscler Thromb Vasc Biol 2006;26:2117-2124.
12. Weiss RM, Lund DD, Chu Y, et al. Osteoprotegerin inhibits aortic valve calcification and preserves valve function in hypercholesterolemic mice. PLoS One 2013;8:e65201.
13. Jiang JQ, Lin S, Xu PC, Zheng ZF, Jia JY. Serum osteoprotegerin measurement for early diagnosis of chronic kidney disease-mineral and bone disorder. Nephrology (Carlton) 2011;16:588-594.

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