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Abstract: Although parathyroid hormone is known to be related with calcium and phosphate metabolism, it has been also reported to have several effects on the cardiovascular system including heart and vessels. However, the detailed pathophysiological mechanisms remain unclear. Clinical studies have indicated that parathyroid hormone is associated with cardiovascular events and mortality not only in patients with chronic kidney disease but also in those without chronic kidney disease. As a possible mechanism, it is thought that parathyroid hormone is associated with the renin-angiotensin-aldosterone system and has direct effects on the cardiovascular system. Therefore, we should pay attention to not only the control of serum phosphate and calcium levels but also the control of serum parathyroid hormone levels, especially in patients with chronic kidney disease. Key Words: Aldosterone, Cardiovascular Disease, Chronic Kidney Disease, Parathyroid Hormone, Renin-angiotensin-Aldosterone System.

Parathyroid hormone (PTH), produced by parathyroid cells, is a crucial regulator related to calcium, phosphate, and vitamin D metabolism. This hormone is one of the key players in the field of chronic kidney disease-mineral bone disorder (CKD-MBD) (1). With declining kidney function, the production of PTH in the parathyroid increases, leading to various clinical problems. One of the most serious clinical problems is cardiovascular disease (CVD) because it is a major cause of death in patients with chronic kidney disease (CKD) (2,3). It is known that PTH can affect the cardiovascular system not only in patients with CKD but also in those without CKD. In 1925, Collip et al. found that PTH is included in the extraction of digested parathyroid tissues and demonstrated that PTH could increase serum calcium levels and decrease blood pressure in their experimental study (4). Since then, various studies have examined the effects of PTH on vascular endothelial cells, vascular smooth muscle cells, and cardiomyocytes. This review summarizes recent data on the effects of PTH on the cardiovascular system.

ROLE OF PARATHYROID HORMONE IN CARDIORENAL ASSOCIATION

PTH and cardiomyocyte

It is known that there are two types of calcium channels, L-type and T-type, on cardiomyocytes, and that PTH acts on an L-type calcium channel (5). An L-type calcium channel is strongly associated with the contraction of cardiomyocytes and the cardiac electrical conduction system. As the detailed mechanisms, PTH increases the entry of calcium ions into the cell by acting on an L-type calcium channel (6,7). Experimental studies using rat cardiomyocytes have shown that the administration of PTH alters cardiac contraction by a change in intracellular calcium concentration and that PTH promotes apoptosis of cardiomyocytes (8,9). These findings indicated that PTH induces oxidative stress and necrotic cell death by promoting mitochondrial
Ca2+ excess, which in the long-term causes or exacerbates myocardial fibrosis.

As a mechanism of PTH-induced cardiac hypertrophy, an activation of protein kinase C (PKC) by this hormone is proposed (10). PTH increases cellular cyclic adenosine monophosphate (cAMP) concentrations via PKC-dependent phosphodiesterase activity and thereby promotes the progression of cardiac hypertrophy through increase in expressions of several cardiac hypertrophy-related genes.

**PTH and atherosclerosis**

There are various studies concerning the effects of PTH on the vascular system. PTH increases cAMP production in vascular smooth muscle cells and leads to vasodilatation through decrease in calcium entry into the cells. PTH receptors also exist on the cell surface membrane of vascular endothelial cells and PTH increases endothelial nitric oxide synthase mRNA and protein expressions and its activity through increased activity of both protein kinase A and PKC pathways (11). As a result, increased nitric oxide production contributes to vasodilatation. Additionally, previous studies have shown that PTH and PTH-related protein suppress the expression of osteogenic markers and calcium deposition (12–14). It is suggested that PTH prevents the progression of vascular calcification by inhibiting BMP2-Msx2-Wnt signal (14,15). Conversely, many clinical studies have demonstrated that high PTH levels are associated with vascular calcification and with higher mortality (16). It is thought that not only PTH but also phosphate, calcium, vitamin D, and other minerals affect the vascular system in clinical settings.

**PTH and renin-angiotensin-aldosterone system**

In addition, there has been recent focus on and clarification of the mechanisms of the association between PTH and the renin-angiotensin-aldosterone system (RAS) (17,18). It has been reported that PTH affects the adrenal gland and thereby increases secretion of aldosterone (19). In contrast, aldosterone increases the secretion of PTH by stimulating mineral corticoid receptor in the parathyroid (20). Furthermore, it is known that aldosterone increases urinary excretion of calcium and thereby decreases serum calcium levels (21). The decrease in serum calcium levels also stimulates the elevation of serum PTH levels.

Parathyroid hormone also increases 1,25 (OH)2D3 by activating 1-alfa-hydroxylase in the proximal tubules of the kidney. 1,25 (OH)2D3 has a direct and indirect cardio-protective effects. As one of the indirect cardio-protective effects, its inhibitory effect on renin is well known (22). Thus, PTH also has the opposite effects on RAS.

**Correlation between parathyroid hormone and cardiovascular disease in the clinical settings**

Japanese national data have shown that the impact of PTH on mortality is weaker compared with that of serum phosphate or calcium levels in Japanese hemodialysis patients (23). However, because these patients have various risk factors, it is very difficult to examine a pure impact of PTH on CVD and mortality in clinical settings. Serum PTH levels are remarkably elevated in these patients; therefore, whether slight elevations in serum PTH levels in patients not on dialysis, patients without CKD, or the general population compared with patients on hemodialysis affect the cardiovascular system remains unknown. To date, there are several clinical studies on the association between PTH and CVD, which give interesting and variable information.

A Swedish study of 958 participants from the general population has reported that elevation of serum PTH levels by 1 SD was associated with a 38% increase in CVD death (24). Other research including two independent community-based cohort studies has reported that PTH was associated with the degree of atherosclerosis and risk of clinically overt atherosclerotic disease after adjustment for established vascular risk factors and mineral metabolism (25).

Furthermore, there is a significant study on the relationship between serum PTH level and number of stenotic coronary arteries (26). The study was cross-sectional and included 476 patients who had undergone coronary angiography according to documented indications and had a coronary lesion greater than 50% stenosis in at least one main vessel. Among the study patients, 183 (38.4%) had PTH ≥ 40 pg/mL, and a significant association between PTH level and severity and number of coronary lesions was observed. In patients with CKD, PTH level was also shown to be associated with an increased incidence of cardiovascular events independent of calcium-phosphorous level (27).

As shown by many experimental studies, the correlation between PTH and cardiac hypertrophy is well known. There are several clinical studies regarding this issue (28,29). Our previous study demonstrated that remarkably higher serum PTH level (≥500 pg/mL) was associated with an increase...
in left ventricular mass index and intraventricular thickness in hemodialysis patients without coronary artery disease (29).

In addition, the results of a meta-analysis regarding the association between serum PTH levels and CVD events also has shown that PTH excess indicated an increased risk for total CVD events: pooled HR (95% CI), 1.45 (1.24–1.71) (Fig. 1) (30). Taken together, even with slight elevations in serum PTH levels, these levels are related to an increased risk for CVD.

### Correlation between parathyroid hormone and the renin-angiotensin-aldosterone system in clinical settings

To explain the complex association between PTH and CVD, it is essential to consider the link between PTH and RAS. It has been reported that in patients with primary aldosteronism, serum PTH levels decrease after either adrenalec-tomy or administration of mineralocorticoid receptor antagonists (31). Conversely, another study has revealed that parathyroidectomy for patients with primary hyperparathyroidism decreases not only serum calcium level but also plasma renin and aldosterone levels (32). Taken together, aldosterone is associated with serum PTH elevation; conversely, PTH is associated with plasma aldosterone level elevation. These results suggest that there is a close interaction between the two hormones. A study including 3074 patients referred for coronary angiography, demonstrated that plasma aldosterone concentration and aldosterone to renin ratio were independently and significantly correlated with serum PTH levels regardless of CKD-MBD parameters and kidney function (33). Furthermore, the results of this study have also revealed that both PAC and PTH were independently associated with cardiovascular mortality, with a potential synergistic interaction. It is well known that RAS is activated in patients with heart failure. In this situation, elevation of plasma aldosterone increases urinary excretion of calcium and thereby increases serum PTH levels. In fact, serum PTH levels were reported to be associated with both all-cause and cardiovascular mortality in that population, independent of left ventricular ejection fraction, NT-proBNP levels, eGFR, and 25-hydroxyvitamin D levels (34).

### Effect of inhibition of parathyroid hormone on CVD

Considering the results of various studies noted above, it is supposed that suppressing serum PTH levels elevation might prevent the progression and occurrence of CVD. Calcimimetics are useful in the suppression of serum PTH level elevation, and there

| Study or Subgroup | Log [Risk Ratio] | SE     | Weight | Risk Ratio | Risk Ratio |
|-------------------|-----------------|--------|--------|------------|------------|
| Anderson et al., 2011 | 0.38526         | 0.100486 | 17.1%  | 1.47 [1.21, 1.79] |           |
| Cawthon et al., 2010 | 0.41211         | 0.307715 | 5.4%   | 1.51 [0.83, 2.76] |           |
| Grandi et al., 2011  | 0.52473         | 0.284223 | 6.1%   | 1.69 [0.97, 2.95] |           |
| Hagström et al., 2009 | 0.60432        | 0.25895  | 7.0%   | 1.83 [1.10, 3.04] |           |
| Jassal et al., 2010  | 0.09531         | 0.108252 | 16.4%  | 1.10 [0.89, 1.36] |           |
| Kestenbaum et al., 2011 | 0.14842       | 0.131145 | 14.5%  | 1.16 [0.90, 1.50] |           |
| Kritchevsky et al., 2012 | 0.57661       | 0.300846 | 5.6%   | 1.78 [0.99, 2.63] |           |
| Pilz et al., 2010    | 0.7031          | 0.134636 | 14.2%  | 2.02 [1.55, 2.63] |           |
| Schierbeck et al., 2011 | 0.64185       | 0.379817 | 3.9%   | 1.90 [0.90, 4.00] |           |
| Taylor et al., 2011  | 0.18232         | 0.195404 | 10.0%  | 1.20 [0.82, 1.76] |           |
| Total (95% CI)      |                 |        | 100.0% | 1.45 [1.24, 1.71] |           |

Heterogeneity: Tau² = 0.03; Chi² = 18.14, df= 9 (P= 0.03); I² = 50%
Test for overall effect: Z = 4.57 (P < 0.0001)

Van Ballegooijen AJ, et al. Am Heart J. 2013;165:655-664

**FIG. 1.** Meta-analysis of the correlation between parathyroid hormone and cardiovascular disease events (29).
are some clinical trials using this agent. A previous study has revealed that vascular endothelial function, cardiac diastolic function, and cardiac hypertrophy were improved with treatment using cinacalcet for 20 weeks in hemodialysis patients (35). It is suggested that the improvement was due to decrease in oxidative stress and increase in nitric oxide as the mechanisms. An experimental study using a CKD animal model has shown that cinacalcet treatment prevented the progression of cardiac fibrosis (36). Furthermore, other experimental studies using a rat CKD model have demonstrated that cinacalcet and etelcalcetide proved to halt the progression of vascular calcification (37–39). Other clinical studies have shown that cinacalcet ameliorated vascular abnormalities, such as abdominal aortic calcification and arterial stiffness (40–42). Taken together, the control of serum PTH levels is crucial in clinical settings. In addition to a PTH-lowering effect, calcimimetics can decrease serum FGF23 levels and thereby reduce CVD events (43). Therefore, calcimimetics also have favorable indirect effects on the cardiovascular system by lowering serum FGF23 levels (44).

CONCLUSION
Japanese Society of Dialysis Therapy guideline recommend that serum concentrations of phosphorus, corrected calcium, and PTH are kept within the target ranges and that control of serum phosphorus should have the highest priority, followed by control of calcium, and then by control of PTH (45). This recommendation is based on the evidence regarding clinical factors related to mortality in Japanese dialysis patients (23). However, this guideline is not meant to minimize the control of PTH. Because PTH is strongly associated with control of serum phosphate and calcium levels, its impact on CVD and mortality is not emphasized in the clinical study. As noted in this review, PTH has several direct and indirect effects on the cardiovascular system (Fig. 2); therefore, it is also crucial to take account of appropriate control of PTH in clinical settings.

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