OA Epidemiology
Open Access

Review

Early Career Academics

A potential role for parathyroid hormone in cardiovascular disease

AJ van Ballegooijen[1*]

Abstract

Introduction

Cardiovascular diseases (CVD) have become one of the major causes of death. Over the past decade, vitamin D has attracted substantial interest towards extra-skeletal role in various disease condition, including CVD. Circulating PTH is a major regulator of bone and mineral metabolism and stimulates the conversion of vitamin D to its most active form. Several studies suggested parathyroid hormone (PTH) not only as a biomarker of vitamin D status but also as an independent cardiovascular risk factor that contributes to the progression of CVD.

The objective of this review is to describe the role of disturbances in PTH in relation to CVD.

Discussion

Growing evidence suggests a link between higher PTH concentrations and CVD. Few studies indicate that PTH excess may influence underlying mechanism of CVD including cardiac biomarkers, cardiac structure and incident hypertension, which in turn may promote cardiovascular disease risk. Based on the total evidence in the field, the beneficial effect of vitamin D supplementation by suppressing PTH on cardiovascular health in the general population still needs to be established. Nonetheless, higher PTH concentrations may be involved in cardiac metabolism and repair, and could play a role in the prevention of cardiac diseases.

Conclusion

Excess PTH is a common finding among older populations. As higher PTH concentrations may be harmful for cardiovascular health, suppression of PTH – either by vitamin D therapy or more specific PTH suppression – might help to prevent cardiac disease and lower CVD rates. Based on the current evidence, there is no reason to change the current recommendation to improve vitamin D status (and subsequently lower PTH status) of the general population with regard to influencing cardiovascular risk.

*Corresponding author
Email: hanne.van.ballegooijen@vu.nl

[1] VU University, Amsterdam, the Netherlands

Introduction

Cardiovascular Diseases

As part of the transition into the 21st century, chronic diseases and specifically cardiovascular diseases (CVD) have become one of the major causes of death and disability in most countries of the world. Trends in CVD demographics indicate that CVD mortality has decreased, since the total number of deaths due to CVD declined over the past two decades[1].

However, the incidence of CVD declined less, which indicates that CVD have become more likely to be non-fatal. The survivors of CVD often develop heart pump failure and loss of heart function in the following years. Consequently, the prevalence of cardiac diseases, including systolic and diastolic heart failure is expected to rise in the coming years[1,2,3].

Despite medical progress, improved treatment and survival from cardiac diseases, no substantial change in the prognosis of heart failure have been established. Patients with heart failure report a lower quality of life than the general population[4] and have a very limited life expectancy. Half of the heart failure patients will die within 4 years. This poses a great burden on the public health system[5]. Therefore, the identification of novel factors that can influence loss of heart function is of paramount importance for future disease prevention.

Although much attention has been given to the leading CVD risk factors, namely smoking, obesity and type 2 diabetes, other factors may also be involved in the pathogenesis and progression of CVD. Disturbances in parathyroid hormone (PTH) are plausibly related to CVD risk in general populations[6].

Vitamin D Metabolism

Vitamin D is an integral part of calcium and bone metabolism and works in conjunction with many factors including parathyroid hormone (PTH) to maintain calcium concentrations within normal physiological ranges (see figure 1 for a simplified overview). Vitamin D, in the form of 1,25(OH)2D increases calcium concentrations by the release of calcium from bone, the absorption of dietary calcium from the small intestine and the stimulation of re-absorption of calcium by the kidney to reduce the loss of calcium via urine. Circulating 1,25(OH)2D works in close concert with PTH.

Low circulating calcium triggers the secretion of PTH from the parathyroid glands, which results in a raise in calcium concentrations. In turn, the increase in calcium inhibits PTH secretion from the parathyroid glands. Circulating PTH stimulates the hydroxylation of 25(OH)D into 1,25(OH)2D in the kidney. To complete the feedback loop, 1,25(OH)2D acts directly on the parathyroid glands to regulate PTH.

Several studies suggested PTH not only as a biomarker of vitamin D status but also as an independent cardiovascular risk factor that contributes to the progression of CVD[7].

Excessive PTH secretion may be due to problems in the parathyroid glands themselves or may occur in response to low calcium concentrations, due to vitamin D or calcium deficiency or reduced kidney function[8].

Parathyroid hormone

In the human body, PTH is a polypeptide hormone secreted by the parathyroid glands[9] with a half-life of approximately 5 minutes[10]. It circulates in several forms and related fragments.

Competing interests: None declared. Conflict of interests: None declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

FOR CITATION PURPOSES: *van Ballegooijen AJ. A potential role for parathyroid hormone in cardiovascular disease. OA Epidemiology 2014 Apr 18;2(1):8.*

OA Epidemiology
Open Access

Review

PTH is regulated by circulating calcium and plays a major role in bone metabolism. Even small decrements in calcium concentrations induce the secretion of PTH from the parathyroid glands. PTH is generated by the chief cells of the parathyroid gland and is released as an 84-amino-acid peptide.

PTH acts by binding to the PTH receptor, a membrane-bound receptor which activates a number of different signalling pathways[11]. PTH receptors are present in bone and kidney, although receptors have been identified in the heart as well[12]. In patients with lower kidney function, phosphate retention may occur, which stimulates PTH secretion. Excess PTH might thereby contribute to the greater cardiovascular mortality risk especially in patients with chronic kidney disease[12].

Excessive PTH secretion may be due to problems in the parathyroid glands themselves or may occur in response to low calcium concentrations, due to vitamin D or calcium deficiency or reduced kidney function[8].

In this review, the focus is on specific biomarkers of the vitamin D metabolism particularly on parathyroid hormone in general populations with slightly elevated PTH concentrations.

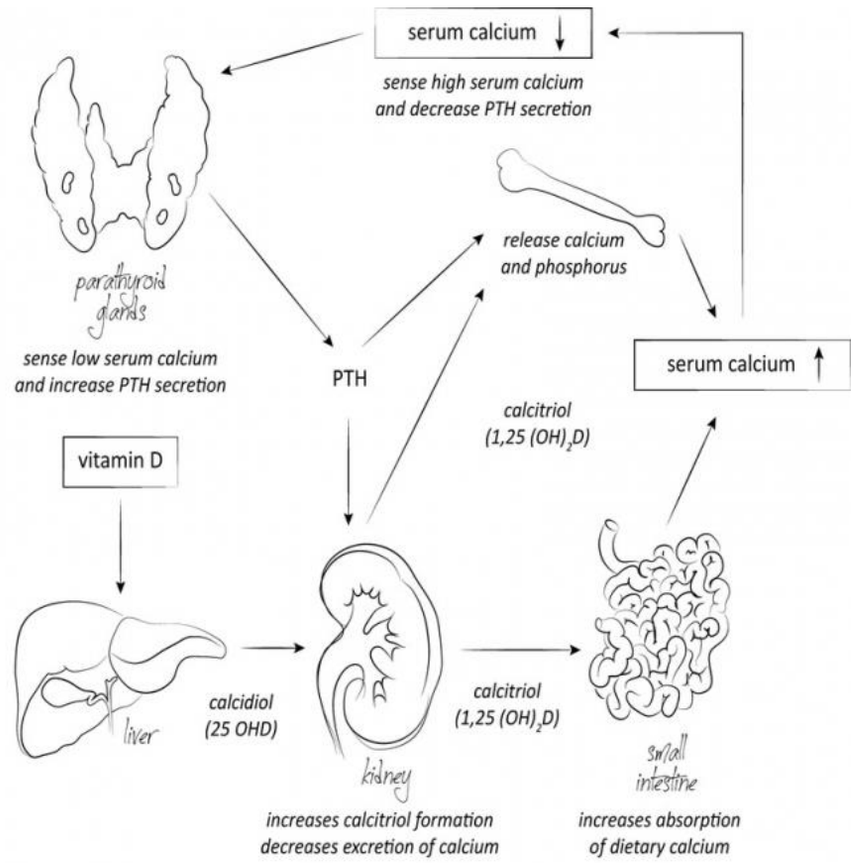

Figure 1: Simplified overview of the calcium-vitamin D-PTH axis.

Discussion

The author has referenced some of its own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

Parathyroid hormone, how does it affect cardiac function?

A growing body of research has identified several potential pathways to explain the deleterious effects of low vitamin D on the cardiovascular system. Proposed mechanisms could be either directly or indirectly and related to different aspects of cardiovascular health. See figure 2 for an overview of proposed mechanisms for PTH and CVD effects. Both vitamin D and PTH receptors are present throughout the body and could play a role in cardiomyocyte, immune and smooth muscle cell function[13,14].

Possible effects of disturbances in the vitamin D metabolism may be explained by direct effects on cardiomyocytes via intracellular signaling[15,16]. Calcium overload in cardiomyocytes may increase mitochondrial malfunction, cardio-myocytes necrosis, as well as activation of interstitial cardiac fibroblasts. These electrical and mechanical abnormalities may exert deleterious effects on cardiomyocytes inducing the secretion of natriuretic peptides (BNP), left ventricular (LV) hypertrophy (greater LV mass) and increase the susceptibility for cardiac diseases[17]. In addition, PTH could activate protein kinase C, which could lead to hypertrophic growth and expression of foetal-type proteins in cardiomyocytes[15]. This hypertrophic effect of PTH might contribute to biochemical changes and higher LV mass and might lead to a decline in ejection fraction[18,19].

Moreover, other indirect pathways related to CVD mechanisms have been described. Vitamin D deficiency and PTH excess may influence blood pressure, e.g. through activation of the renin-angiotensin system, higher levels of aldosterone, impaired arterial function due to loss of arterial elasticity, reduced systolic function, and the regulation of inflammatory cytokines[20,21]. Taken all together, both direct and indirect pathways may explain why disturbances in vitamin D metabolism could potentially increase the risk of cardiac diseases.

Parathyroid hormone and Cardio-vascular Disease

Recent studies have shown links between disturbances in PTH metabolism reflected by too high PTH concentrations and the presence of CVD

Competing interests: None declared. Conflict of interests: None declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

OA Epidemiology
Open Access

Review

events[22,23]. The majority of individuals with higher PTH levels do not feel or notice any symptoms; however chronically elevated PTH levels are associated with chronic kidney disease, all-cause and cardio-vascular mortality.

Associations between vitamin D and CVD may only be found because of its association with PTH. This challenges previous vitamin D hypotheses. A meta-analyses pointed out that higher PTH concentrations are associated with an increased risk of CVD events[6]. Serum PTH appears to be associated with different types of CVD such as ischemic heart disease, diastolic heart failure, and peripheral vascular disease. It is therefore plausible that circulating PTH influences multiple CVD pathways.

Underlying CVD mechanisms

Growing evidence suggests a link between higher PTH concentrations and CVD[7,24]. The majority of previous studies did not distinguish between different heart diseases while CVD pathophysiology is known to be divers. To reduce CVD risk, it is crucial to explore and distinguish underlying PTH-related CVD pathways. Studying underlying mechanisms could provide insight into disease mechanisms and may be important for developing future preventive strategies. Few studies indicate that PTH excess may influence underlying mechanism of CVD including cardiac biomarkers, cardiac structure and incident hypertension[22,25,26], which in turn may promote cardiovascular disease risk.

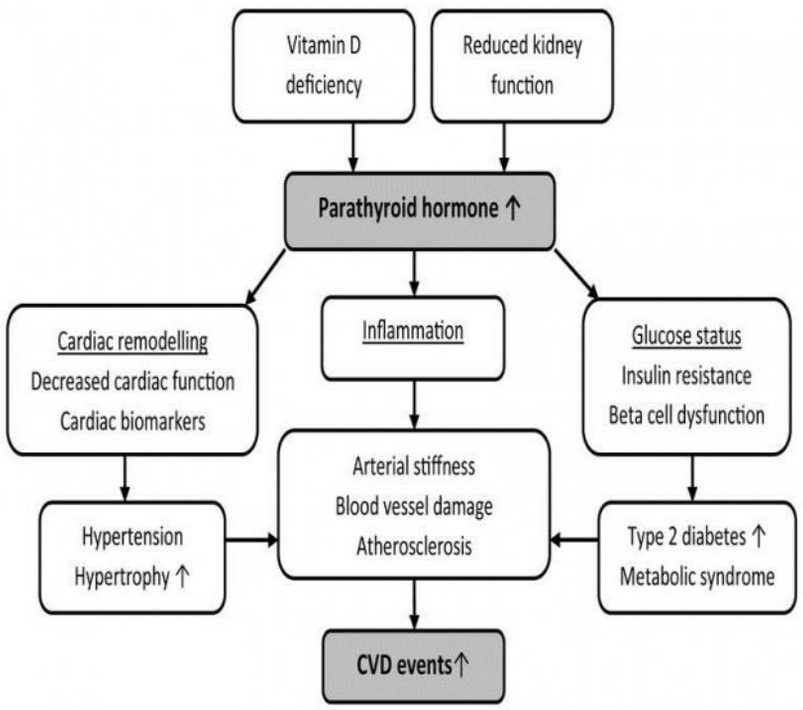

Figure 2: Proposed mechanisms for parathyroid hormone related CVD risk.

Suggestions for future research

However, the mechanisms by which PTH influences CVD risk are still largely unknown. There appears to be a knowledge gap in the literature regarding the low number of prospective studies for PTH and intermediate outcomes.

Therefore, more research is needed to explore associations with intermediate cardiac outcomes. In particularly, prospective studies with a long follow up time (>10 y) would be valuable to capture long-term effects that cannot be covered by most clinical trials. These results of epidemiological studies yield relevant information on dose-response and type of study population for future research, although the generalizability of these results to populations with different age groups, ethnicities or individuals with co-morbid conditions should be done with caution. Therefore, replication of prospective evidence is crucial to identify individuals that would potentially benefit. The growing body of evidence forms the basis to design clinical and public health intervention studies.

The next step is to substantiate whether the relationships between disturbances in vitamin D metabolism and CVD are truly causal. Well-designed, randomized controlled trials are therefore warranted to confirm whether provision of an inexpensive vitamin D supplement favourably affects CVD risk factors and results in less CVD events.

If the association between PTH and cardiovascular health indicates a causal pathway and if PTH mediates the vitamin D effect, vitamin D may impact CVD risk in a specific population only to the extent that it lowers PTH[27].

Many factors can influence the effect a vitamin D intervention would have on PTH concentrations, including underlying 25(OH)D status, vitamin D dose, the dose-response relationship between 25(OH)D and PTH, calcium intake and other underlying population factors, such as age, sex, body mass, genetics and medication use[28]. It is advisable that future RCTs focus on those populations with low 25(OH)D concentrations and with elevated PTH concentrations that will be likely to benefit to benefit from vitamin D treatment. Future studies should keep in mind an appropriate time window to capture the effect of cardiac outcomes on short- and long-term mechanisms.

Some large randomized controlled trials with composite endpoints are on-going and results are expected within 5 years: DO-HEALTH (EU), the FIND dose-response trial (Finland), the VITA Study (Australia), and the Vital Study (USA).

Genetic differences and CVD risk

Recent studies suggest that inter-individual variability in vitamin D metabolism may alter clinical consequences of serum 25(OH)D. Known associations of low serum

Competing interests: None declared. Conflict of interests: None declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

OA Epidemiology
Open Access

Review

25(OH)D with clinical outcomes may vary according to genetic differences in the vitamin D receptor measured by single-nucleotide polymorphisms over long-term of follow-up[29].

Further work is needed to replicate these observed associations and to enhance knowledge of how variation in vitamin D metabolism genes stratifies individuals to their susceptibility to vitamin D deficiency and thus identify individuals who may benefit most from vitamin D therapy.

While these novel findings of lower 25(OH)D may contribute to a better understanding of the biological impact of genetic variation within the vitamin D receptor, other factors part of this complex endocrine system might be important determinants as well. The genetic field for PTH metabolism is still in its infancy and knowledge of how variation in PTH metabolism genes stratifies individuals to their susceptibility to CVD risk is needed.

Can PTH be used as an emerging biomarker for adverse cardiovascular events?

Recent studies, have suggested that elevated PTH concentrations predict adverse cardiovascular outcomes[6,7,30].

Although PTH might have prognostic information, the clinical utilities of PTH as a promising biomarker in predicting cardiac dysfunction and CVD events needs to be established. The strength of a biomarker is its ability to guide the clinician in decision management[31]. Until now, it remains unclear whether changes in PTH during the clinical course have any added value. These limitations need to be addressed before we can use PTH as a predictor in clinical practice. Furthermore, whether PTH may provide incremental prognostic information not provided by other established biomarkers as BNP or Troponin T, is unclear. These aspects require further assessment before PTH can be used as a predictor of cardiac dysfunction and CVD risk.

Recommendations

Findings of circulating PTH and subclinical measures of cardiovascular health should be replicated in multi-ethnic populations, and among populations with diverse disease states and age groups.

More prospective studies are needed to better define changes in tissue specific characteristics of heart health including scar tissue and fibrosis to give more insight into the underlying mechanisms that might lead to CVD events.

Future work should look at the prognostic value of PTH as a risk marker of CVD in prediction models and investigate whether the association remains statistically significant after adjusting for the well-known risk factors as smoking, obesity and type 2 diabetes. Well-designed randomized controlled trials are awaited to evaluate whether individuals with high PTH con-centrations benefit from therapeutic approaches targeted to decrease PTH concentrations and reduce CVD events.

Perspectives

Circulating PTH is a major regulator of bone and mineral metabolism. Emerging evidence suggests that excess PTH is a common findings among older populations. The prevalence of cardiac diseases, including heart failure is a great burden on the public health system. Due to the aging society the prevalence of CVD will likely increase in the upcoming years[1,2,3]. Based on the total evidence in the field, the beneficial effect of vitamin D supplementation by suppressing PTH on cardiovascular health in the general population still needs to be established. Nonetheless, higher PTH concentrations may be involved in cardiac metabolism and repair, and could play a role in the prevention of cardiac diseases.

Conclusion

As higher PTH concentrations may be harmful for cardiovascular health, suppression of PTH – either by vitamin D therapy or more specific PTH suppression – might help to prevent cardiac disease and lower CVD rates. Based on the current evidence, there is no reason to change the current recommendation to improve vitamin D status (and subsequently lower PTH status) of the general population with regard to influencing cardiovascular risk.

References

1. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, et al. Executive Summary: Heart Disease and Stroke Statistics--2013 Update: A Report From the American Heart Association. Circulation 2013;127: 143-152.
2. Bleumink GS, Knetsch AM, Sturkenboom MC, Straus SM, Hofman A, Deckers JW, et al. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure The Rotterdam Study. Eur Heart J 2004; 25:1614-9.
3. Goldberg RJ, Spencer FA, Farmer C, Meyer TE, and Pezzella S. Incidence and hospital death rates associated with heart failure: a community-wide perspective. Am J Med 2005;118:728-34.
4. Juenger J, Schellberg D, Kraemer S, Haunstetter A, Zugck C, Herzog W, et al. Health related quality of life in patients with congestive heart failure: comparison with other chronic diseases and relation to functional variables. Heart 2002;87:235-41.
5. Robertson J, McElduff P, Pearson SA, Henry DA, Inder KJ, and Attia JR. The health services burden of heart failure: an analysis using linked population health data-sets. BMC Health Serv Res 2012;12:103.
6. van Ballegooijen AJ, Reinders I, Visser M, and Brouwer IA. Parathyroid hormone and cardiovascular disease events: A systematic review and meta-analysis of prospective studies. Am Heart J 2013;165:655-664.
7. Kestenbaum B, Katz R, de Boer I, Hoofnagle A, Sarnak MJ, Shlipak MG, et al. Vitamin d, parathyroid hormone, and cardiovascular events among older adults. J Am Coll Cardiol 2011;58:1433-41.
8. Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and

Competing interests: None declared. Conflict of interests: None declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

OA Epidemiology
Open Access

Review

fractures and therapeutic implications. Endocr Rev 2001;22: 477-501.
9. Fraser WD. Hyperparathyroidism. Lancet 2009;374:145-58.
10. Bieglmayer C, Prager G, and Niederle B. Kinetic analyses of parathyroid hormone clearance as measured by three rapid immunoassays during parathyroid-ectomy. Clin Chem 2002;48:1731-8.
11. Swarthout JT, D'Alonzo RC, Selvamurugan N, and Partridge NC. Parathyroid hormone-dependent signaling pathways regulating genes in bone cells. Gene 2002;282:1-17.
12. Potthoff SA, Janus A, Hoch H, Frahnert M, Tossios P, Reber D, et al. PTH-receptors regulate nor-epinephrine release in human heart and kidney. Regul Pept 2011;171:35-42.
13. Absi M and Ward DT. Increased endothelin-1 responsiveness in human coronary artery smooth muscle cells exposed to 1,25-dihydroxyvitamin D(3). Am J Physiol Cell Physiol 2013;304:C666-72.
14. Burgazli KM, Foerster N, Mericliler M, Chasan R, Parahuleva M, and Erdogan A. Effects of parathyroid hormone-related peptide on the large conductance calcium-activated potassium channel and calcium homeostasis in vascular smooth muscle cells. Postgrad Med 2014; 126:76-85.
15. Schluter KD and Piper HM. Cardiovascular actions of parathyroid hormone and parathyroid hormone-related peptide. Cardiovascular Research 1998;37:34-41.
16. Chen S, Law CS, Grigsby CL, Olsen K, Hong TT, Zhang Y, et al. Cardiomyocyte-specific deletion of the vitamin d receptor gene results in cardiac hypertrophy. Circulation 2011;124:1838-47.
17. Pilz S, Tomaschitz A, Drechsler C, Dekker JM, and Marz W. Vitamin D deficiency and myocardial diseases. Mol Nutr Food Res 2010;54:1103-13.
18. Piovesan A, Molineri N, Casasso F, Emmolo I, Ugliengo G, Cesario F, et al. Left ventricular hypertrophy in primary hyperparathyroidism. Effects of successful parathyroidectomy. Clin Endocrinol 1999;50:321-8.
19. van Ballegooijen AJ, Visser M, Cotch MF, Arai AE, Garcia M, Harris TB, et al. Serum vitamin D and parathyroid hormone in relation to cardiac structure and function: the ICELAND-MI substudy of AGES-Reykjavik. J Clin Endocrinol Metab 2013;98:2544-52.
20. Pirro M, Manfredelli MR, Helou RS, Scarponi AM, Schillaci G, Bagaglia F, et al. Association of parathyroid hormone and 25-OH-vitamin D levels with arterial stiffness in postmenopausal women with vitamin D insufficiency. J Atheroscler Thromb 2012;19:924-31.
21. Tomaschitz A, Ritz E, Pieske B, Rus-Machan J, Kienreich K, Verheyen N, et al. Aldosterone and parathyroid hormone interactions as mediators of metabolic and cardiovascular disease. Metabolism 2014;63:20-31.
22. Pilz S, Tomaschitz A, Drechsler C, Ritz E, Boehm BO, Grammer TB, et al. Parathyroid hormone level is associated with mortality and cardiovascular events in patients undergoing coronary angiography. Eur Heart J 2010;31:1591-8.
23. Hagstrom E, Hellman P, Larsson TE, Ingelsson E, Berglund L, Sundstrom J, et al. Plasma parathyroid hormone and the risk of cardiovascular mortality in the community. Circulation 2009;119: 2765-71.
24. Anderson JL, Vanwoerkom RC, Horne BD, Bair TL, May HT, Lappe DL, et al. Parathyroid hormone, vitamin D, renal dysfunction, and cardiovascular disease: Dependent or independent risk factors? Am Heart J 2011;162:331-9.
25. Tomaschitz A, Pilz S, Ritz E, Grammer T, Drechsler C, Boehm BO, et al. Independent association between 1,25-dihydroxyvitamin D, 25-hydroxyvitamin D and the renin-angiotensin system: The Ludwigshafen Risk and Cardiovascular Health (LURIC) study. Clin Chim Acta 2010;411:1354-60.
26. Taylor EN, Curhan GC, and Forman JP. Parathyroid hormone and the risk of incident hypertension. J Hypertens 2008;26:1390-4.
27. Giovannucci E. Cholecalciferol Treatment in Older Patients With Isolated Systolic Hypertension. JAMA Intern Med 2013.
28. Giovannucci E. Cholecalciferol treatment in older patients with isolated systolic hypertension. JAMA Intern Med 2013;173:1680-1.
29. Levin GP, Robinson-Cohen C, de Boer IH, Houston DK, Lohman K, Liu Y, et al. Genetic variants and associations of 25-hydroxyvitamin D concentrations with major clinical outcomes. JAMA 2012;308:1898-905.
30. Hagstrom E, Ingelsson E, Sundstrom J, Hellman P, Larsson TE, Berglund L, et al. Plasma parathyroid hormone and risk of congestive heart failure in the community. Eur J Heart Fail 2010;12:1186-92.
31. van Kimmenade RR and Januzzi JL, Jr. Emerging biomarkers in heart failure. Clin Chem 2012;58:127-38.

Competing interests: None declared. Conflict of interests: None declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.