A potential role for parathyroid hormone in cardiovascular disease

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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.

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.

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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 function³.

Parathyroid hormone

In the human body, PTH is a polypeptide hormone secreted by the parathyroid glands with a half-life of approximately 5 minutes¹⁰. It circulates in several forms and related fragments.
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. PTH receptors are present in bone and kidney, although receptors have been identified in the heart as well. 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.

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.

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.

**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.

Possible effects of disturbances in the vitamin D metabolism may be explained by direct effects on cardiomyocytes via intracellular signaling. Calcium overload in cardiomyocytes may increase mitochondrial malfunction, cardiomyocytes 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. In addition, PTH could activate protein kinase C, which could lead to hypertrophic growth and expression of foetal-type proteins in cardiomyocytes. This hypertrophic effect of PTH might contribute to biochemical changes and higher LV mass and might lead to a decline in ejection fraction.

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. 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 Cardiovascular Disease**

Recent studies have shown links between disturbances in PTH metabolism reflected by too high PTH concentrations and the presence of CVD.
events. 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. 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. 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, which in turn may promote cardiovascular disease 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 particular, 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.

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. 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 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 ongoing 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

Figure 2: Proposed mechanisms for parathyroid hormone related CVD risk.
Can PTH be used as an emerging biomarker for adverse cardiovascular events?

Recent studies, have suggested that elevated PTH concentrations predict adverse cardiovascular outcomes. Although PTH might have prognostic information, the clinical utilities of PTH as a promising biomarker in predicting cardiac dysfunction and CVD events need to be established. The strength of a biomarker is its ability to guide the clinician in decision management. Until now, it remains unclear whether changes in PTH concentrations in 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.

Perspectives

Circulating PTH is a major regulator of bone and mineral metabolism. Emerging evidence suggests that excess PTH is a common finding 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. 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.

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