Primary hyperparathyroidism and cardiovascular risk. Is there a connection?

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Abstract
In primary hyperparathyroidism parathormone (PTH) is secreted autonomously and produce increase of calcium and decrease of phosphorus in the serum of the affected patients. In this study the newer facts in the medical literature about the influence of primary hyperparathyroidism in cardiovascular system are presented. Big studies have investigated the role of several factors affected in primary hyperparathyroidism. It seems that the increase of PTH affects the cardiovascular system in various ways. But there is a debate about the mild cases of hyperparathyroidism and short-standing disease.

Key words: parathyroid glands; hyperparathyroidism; adenoma; cardiovascular

Introduction
The parathyroid glands are 4 in 80-87% of cases in humans, but in the rest of cases the number of parathyroid glands vary from 2 to 8. The main role of these glands is the produce of parathormone (PTH). This hormone with vitamin D and calcitonin are the main coordinators of the metabolism of calcium in human body.

The diseases of the parathyroid glands can be divided based on the amount of PTH secretion and their function. Only one gland or all of these glands may overfunction or hypofunction. In the latter case we have to do with hypoparathyroidism and in the first case with hyperparathyroidism [1, 2].

Primary hyperparathyroidism is a common disease as it is the third endocrine disease in frequency, after diabetes mellitus and hyperthyroidism. It is estimated to occur in 0.1-0.3% of the general population. It is thought to occur more commonly in elderly, in females and after the irradiation of the head and neck area [3, 4]. A single adenoma is the main reason of primary hyperparathyroidism in 80-85% of cases. Clinical manifestations of this endocrine disease seem to be affected from the weight of the adenoma of the parathyroid gland and the longstanding disease [1, 2, 5].

In this study we are going to resume the current opinions in medical literature for the role of the hypersecretion of PTH in primary hyperparathyroidism in cardiovascular system.

Primary hyperparathyroidism as a hyperfunction state of parathyroid glands leads to increased calcium and decreased phosphorus in the serum of the patients. The PTH is usually increased and vitamin D is usually lower than normal or normal.

Clinical manifestations and symptoms of primary hyperparathyroidism may be mild or severe, profound or asymptomatic. The main characteristic of this disease is that there may be exacerbation and recession and there are no characteristic symptoms attributed to it. This phenomenon results to the fact that these patients remain underdiagnosed for many years, especially in the past. General symptoms of primary hyperparathyroidism are lose of body weight, fatigue, anorexia, musculoskeletal, osteoporosis, urinary stones, psychiatric symptoms and many other [1, 2, 6, 7].

In cardiovascular system, symptoms and manifestations attributed to primary hyperparathyroidism are myocardial infarction, angina, arrhythmias, hypertension, heart failure, calcifications of cardiac valves.

In 1985 the first thoughts about the relation between primary hyperparathyroidism and increased cardiovascular risk have been published from Ronni-Sivula et al. They performed a study in patients with primary hyperparathyroidism and increased calcium and they concluded that these patients have increased mortality from cardiovascular disorders [8].

In the most recent studies which examine the cardiovascular risk in patients with primary hyperparathyroidism there is controversy about the real risk. This fact is attributed to the differences of the study groups of every study. In studies with big number of patients (v=4461) the conclusion is that the cardiovascular risk in patients with primary hyperparathyroidism is increased. But smaller studies (v=435) do not have the same results [9, 10].

The factors which independently are associated with cardiovascular risk in the patients with primary hyperparathyroidism who undergo parathyroidectomy are the value of PTH preoperatively, the levels of serum calcium preoperatively and the weight of the adenoma of the parathyroid glands [9, 11].

Hypertension is found more commonly in the patients with primary hyperparathyroidism than the general population. Echocardiography can also reveal very often calcification of cardiac valves, especially the aortic and mitral in patients with elevated PTH and in primary hyperparathyroidism. Microcalcifications could also be seen in the myocardium of these patients [1, 2, 6].
The study of Hvarfner et al in 1989 noticed the important role of calcium in hypertension. This study revealed that there is substantial and significant increase of blood pressure, both diastolic and systolic after the infusion of calcium in subjects with normal or near normal blood pressure. In another study in healthy subjects the increase of serum calcium levels after infusion of calcium resulted to dose-related decrease of the diastolic capability of endothelium and therefore increase of systolic blood pressure [12, 13].

In contrary to the study of Dominiczak et al in 1990, studies of Schiffl et al in 1997 and Fardella & Rodriguez-Portales in 1995 showed that the concentration of calcium inside platelets is raised in patients with primary hyperparathyroidism. Some of these patients had hypertension and some did not. After a successful parathyroidectomy the normalization of serum PTH resulted also to normalization of calcium inside platelets. In these patients with primary hyperparathyroidism it seems that calcium intracellular levels are closely related to the levels of PTH. So we can assume that an elevated PTH characterize a pre-hypertensive state in patients with primary hyperparathyroidism and with normal blood pressure levels [14, 15]. Moreover, the infusion of PTH in healthy subjects can cause hypercalcemia and hypertension. There is also known the close relationship between the increase of PTH serum levels and the activation of the renin-angiotensin-aldosterone system. The most of the investigators believe that the activation of this system is responsible for the cardiovascular complications and the hypertension in patients with primary hyperparathyroidism. But after the parathyroidectomy the improvement of hypertension or the other cardiovascular disorders is not clear [12-16].

In patients with primary hyperparathyroidism cardiac remodeling is revealed in echocardiography. In several studies distension of the left cardiac chambers and especially the left ventricle is seen. A parallel hypertrophy of the left ventricle is also seen in most of the times.

It is estimated that in 81.6% of the patients with primary hyperparathyroidism there is a mild hypertrophy of the intraventricular septum and in 78.2% there is hypertrophy of the posterior cardiac wall. Of course this hypertrophy is related with hypertension, because a positive correlation exists. Some studies were designed to assess the efficacy of parathyroidectomy and they revealed that in 6 and later in 14 months postoperatively hypertrophy of the intraventricular septum and the posterior cardiac wall was regressed in the majority of the patients. These patients did not have history of hypertension. Regression of hypertension did not observed [17, 18].

Preoperatively in patients with primary hyperparathyroidism some cardiac structural deficiencies have been observed. The microcalcifications could be observed during echocardiography in myocardium, especially in intraventricular septum in 65% of the patients. Calcification of the cardiac valves could also be seen. Aortic valve is calcified in 57-63% of patients with primary hyperparathyroidism. Overall, calcification of the aortic valve could cause in 14% of the cases a mild or medium stenosis [17]. The next valve which is affected from calcification in primary hyperparathyroidism is mitral. In 33-49% of patients with primary hyperparathyroidism there are evidence of calcification in mitral valve, with a subsequent stenosis in 22% of these patients. After a year after successful parathyroidectomy these calcifications do not seem to decline. It is proved that after the operation there is no progress neither regression [17-19].

Generally, PTH has the main causative role in cardiovascular disorders in primary hyperparathyroidism. In many studies PTH seems to have a positive correlation with cardiovascular risk and morbidity. Anderson et al study and Hoorn study from The Netherlands are the bigger of these cohort studies. Hoorn study lasted approximately 13 years. 2484 patients participated in this study and the median follow-up was 7.8 years. This study resulted that the levels of PTH increased in both univariate and multivariate analyses the risk of death of general and cardiovascular causes [20]. H. Altay et al in their study are concluding that PTH could have a very important role in assessing cardiac failure state as it could differentiate the patients who are in increased risk for complications and deterioration of cardiac failure. Furthermore, PTH can have prognostic role in cardiac failure and could lead therapy based to level of PTH values in serum. This is a fact pointed in study of D. Gruson et al [21-23].

The influence of PTH and vitamin D in cardiac function and structure was studied in ICELAND-MI study in 969 persons. This cohort study was performed in a population in Iceland. The cardiac structure and function were assessed related to levels of PTH and vitamin D. Vitamin D in this study population did not seem to have any influence in cardiac function. This was not happening with PTH. Increased PTH seemed to produce smaller ejection fraction and distension of the left ventricle. Smaller studies had the same results [24-28].

Conclusions:
After the search of the studies in medical literature we can conclude that there is no clear answer to the next questions:
- If there are atypical or low intensity symptoms or there is complete lack of symptoms in primary hyperparathyroidism, what is the chance of the cardiovascular system to be affected?
- How many time the cardiovascular system needs to be affected in an environment of elevated PTH and calcium?
- Does the surgery regress or stabilize the cardiovascular disorders and when?

These questions are the reason for new studies to be performed in the future which will have to prove or not the close relationship of the factors who are infected in primary hyperparathyroidism and cardiovascular system.

References:


