Research Article

The Importance of Correlation between Aldosterone and Parathyroid Hormone in Patients with Primary Hyperparathyroidism

Branka Milicic Stanic,1,2 Branislava Ilincic,2,3 Radmila Zeravica,2,3 Dragana Milicic Ivanovski,4 Velibor Cabarkapa,2,3 and Romana Mijovic2,3

1Department of Medicine, Georgetown University Medical Center, 4000 Reservoir Road, NW, Washington, DC 20057, USA
2University of Novi Sad, Faculty of Medicine, Hajduk Veljkova 3, Novi Sad 21000, Serbia
3Center for Laboratory Medicine, Clinical Center of Vojvodina, Hajduk Veljkova 1–9, Novi Sad 21000, Serbia
4Center for Pathophysiology of Breathing and Respiratory Sleep Disorders, The Institute for Pulmonary Diseases of Vojvodina, Put dr Goldmana 4, Sr Kamenica 21204, Serbia

Correspondence should be addressed to Branka Milicic Stanic; bs1132@georgetown.edu

Received 17 June 2022; Accepted 21 October 2022; Published 7 November 2022

Academic Editor: Giorgio Borretta

Copyright © 2022 Branka Milicic Stanic et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

In primary hyperparathyroidism, an increased risk of developing the cardiovascular disease may exist due to increased activity of the renin-angiotensin-aldosterone system. The aim of this study was to evaluate the relationship between parathyroid hormone and aldosterone in patients with primary hyperparathyroidism. The study included 48 patients with primary hyperparathyroidism and 30 healthy subjects who matched age and gender to the study group. This study was conducted at the Center for Laboratory medicine, Clinical center of Vojvodina, Novi Sad, Serbia. In addition to clinical data and laboratory determination of the concentration of total and ionized calcium, phosphorus, measurements of parathyroid hormone, vitamin D, direct renin, and aldosterone were performed by the method of chemiluminescent technology. Compared to the controls, the study group had statistically significantly higher values of aldosterone ($p < 0.028$), total calcium ($p < 0.01$), ionized calcium ($p = 0.003$) and parathyroid hormone ($P \leq 0.001$). Serum aldosterone and parathyroid hormone levels were correlated positively in patients with primary hyperparathyroidism ($r = 0.509, p < 0.05$). A statistically significant positive correlation between renin and parathyroid hormone ($r = 0.688, p < 0.05$) and renin and calcium ($r = 0.673, p < 0.05$) was determined in hyperparathyroid patients. In multivariate regression analysis, the strongest predictive variable of aldosterone secretion was parathyroid hormone ($p = 0.011$). An independent relationship between parathyroid hormone and aldosterone in patients with primary hyperparathyroidism and the correlation between renin and parathyroid hormone as well as with calcium indicate not only the direct but also the indirect associations between parathyroid hormone and aldosterone in primary hyperparathyroidism. These findings may represent another possible model of renin-angiotensin-aldosterone-induced organ damage.

1. Introduction

Parathyroid glands synthesize the parathyroid hormone (PTH) which is the primary regulator of calcium homeostasis. After the structure and function of the PTH hormone was clarified, it became clear that PTH also manifests other effects in addition to the action on the bones and kidney, such as the effect on the cardiovascular system [1, 2].

PTH is a peptide hormone secreted by the chief cells of the parathyroid glands [3]. The major physiological regulator of PTH secretion is the concentration of serum ionized calcium ($\text{Ca}^{2+}$) [4]. $\text{Ca}^{2+}$ is a ligand for the calcium-sensitive receptor (CaSR), presented on the surface of the parathyroid glands, C-cells of the thyroid gland, and also in the kidneys and the brain. Decreased concentration of calcium ($\text{Ca}^{2+}$) in the blood will be registered by CaSR receptors and trigger
activity in parathyroid cells that leads to the secretion of already synthesized hormone stored in the secretory granules of the main cells of the parathyroid gland [1, 5]. In addition to calcium, other regulators of PTH secretion have been identified such as primarily phosphates and calcitriol but also magnesium, catecholamines, fibroblast growth factor 23 (FGF-23)/klotho system, estrogen, etc. [4].

PTH interacts with type 1 PTH receptor (PTH/PTHrP receptors) located primarily on the plasma membrane of the renal tubules and bone cells-osteoblasts but also in other tissues including fibroblasts, chondrocytes, smooth muscle cells of the blood vessels, cardiomyocytes, adipocytes, and placental trophoblasts [2, 6].

PTH increases the level of calcium by renal tubular reabsorption, bone resorption and promotion of conversion of 25 (OH)D to the active metabolite of vitamin D-1, 25 (OH)2D3 which further stimulates intestinal Ca absorption [1].

Hyperparathyroidism is a common endocrine disorder and various studies revealed an estimated prevalence of primary hyperparathyroidism (pHPT) in the general population of 0.5% to 1% increasing with age over 2% [7, 8].

Primary hyperparathyroidism is a disease caused by overactive secretion of PTH characterized by hypercalcemia, hypophosphatemia, symptoms of osteoporosis, kidney stones, and numerous neurologic and cardiovascular disorders [9].

There are numerous of evidences that patients with adenoma or parathyroid gland hyperplasia, i.e., primary hyperparathyroidism, have an increased risk of developing a cardiovascular disease [10].

PTH has a positive inotropic effect, and in adult cardiomyocytes, PTH binding activates G-protein signaling, increasing calcium influx into cardiac cells through beta-adrenergic stimulation [11]. The important role of PTH is maintaining normal cardiac contractility by having a positive chronotropic effect in cardiomyocytes [12].

The results of numerous studies have indicated that PTH promotes Ca2+ entry into cells, increasing vasoconstriction and causing arterial hypertension [13]. Also, PTH promotes vascular and cardiac remodeling, causes vascular stiffness, and increases cardiac afterload [14]. Cardiovascular morbidity and mortality are increased in both primary and secondary hyperparathyroidism, with a 25–70% prevalence of hypertension in primary hyperparathyroidism, according to different sources [15–17]. There are several predisposing mechanisms that affect the onset of hypertension in primary hyperparathyroidism: PTH leads to increased synthesis of 1, 25 (OH)2 vitamin D, which then leads to increased calcium influx into the smooth muscle cells of the blood vessels causing elevated vascular tone and arterial hypertension. PTH has been shown to have a proinflammatory effect on blood vessels which contributes to atherosclerosis of blood vessels and the development of hypertension [18–22].

Aldosterone is a mineralocorticoid that is a major regulator of extracellular fluid volume and potassium metabolism [1]. The biological effects of angiotensin II and aldosterone are mediated through the mineralocorticoid receptor (MCR) agonists angiotensin type 1 and type 2 receptors (AT1 and AT2R) [24]. Hypersecretion of aldosterone increases sodium reabsorption in the distal tubules, and potassium and hydrogen secretion, leading to hypervolemia, arterial hypertension with imbalance of ionic composition, and acid-base status. Due to increased aldosterone production, numerous adverse cardiovascular, renal, and cerebrovascular effects result from the activation of mineralocorticoid receptors, which are widespread in endothelial cells, smooth muscle cells, cardiomyocytes, parathyroid cells, endothelial progenitor cells, and neutrophils [25]. According to experimental data, aldosterone by a rapid, so-called nongenomic effects, that involve activation of second messenger pathways, in various non epithelial tissues increases oxidative stress, inflammation, and collagen remodeling leading to endothelial dysfunction, ventricular hypertrophy, cardiac fibrosis, heart failure, and kidney damage and is directly associated with the development of atherosclerosis [26].

It is very important to understand the normal physiological relationship between the RAAS and PTH because it has been previously established that dysregulation of aldosterone as well as PTH plays an important role in the development and progression of cardiovascular disease.

Recent studies revealed that calcium and PTH have been implicated in regulating the RAAS, and the RAAS, in turn, has been implicated in regulating these calcium-regulatory hormones.

Recent observational studies in individuals with primary hyperaldosteronism (PA) suggest that excess aldosterone may result in hyperparathyroidism [18, 27]. However, the interaction between these two hormones and their potential role in target organ damage are less well known.

There are an increasing number of studies indicating a two-way and positive relationship between the RAAS system and PTH [28].

1.1. Research Objective. The aim of the study was to examine the relationship between circulating serum levels of parathyroid hormone and aldosterone in patients with primary hyperparathyroidism.

2. Material and Methods

2.1. Respondents and Study Design. This cross-sectional study was conducted in the period from February 2017 to April 2018, in the Clinical Center of Vojvodina, Novi Sad, Serbia.

48 patients who were biochemically diagnosed with primary hyperparathyroidism were included confirmed by positive sestamibi radionuclide scan.

The basic criteria for exclusion of respondents were verified metabolic bone disease, hyperaldosteronism, Cushing’s syndrome, pheochromocytoma, type 1 and type 2 diabetes mellitus, autoimmune diseases, previously proven...
related clinical features, medications), was performed with the
Kolmogorov–Smirnov test. Comparison of clinical characteristics,
which was examined by Kolmogorov–Smirnov test. Comparison of clinical characteristics, a normal distribution, which was examined by Kolmogorov–Smirnov test. Compared to the control group, the study group had statistically significantly higher levels of aldosterone \((p = 0.028)\), total calcium \((p = 0.01)\), ionized calcium \((p = 0.003)\) and PTH \((p \leq 0.001)\), while statistically significantly lower levels in the study group were for phosphorus \((p = 0.003)\) and 25 \((OH)\) D \((p = 0.04)\) (Table 2).

In the study group, correlation analysis shows a positive
correlation between renin and PTH \((r = 0.688, p < 0.05)\)
(Figure 1); renin and calcium \((r = 0.673, p < 0.05)\) and renin
and ionized calcium \((r = 0.641, p < 0.05)\). Aldosterone showed a statistically significant positive correlation with
PTH \((r = 0.509, p < 0.05)\) (Figure 2) (Table 3).

Correlation analysis in the control group revealed that
there was no significant correlation between renin and PTH
\((p > 0.05)\), calcium \((p > 0.05)\) and ionized calcium \((p > 0.05)\). Also, aldosterone did not show a positive correlation with
PTH \((p > 0.05)\), as well as with total and ionized calcium
\((p > 0.05; p > 0.05)\) (Table 3).

No significant correlation was found between 25 \((OH)\)D and other parameters.

In patients with pPTH, linear regression analysis further
revealed that PTH levels were significantly associated with
aldosterone \((\beta = 2.710; p = 0.011)\).

4. Discussion
In our study, the patients with primary hyperparathyroidism
had statistically significantly higher values of PTH \((p \leq 0.001)\),
total calcium \((p = 0.01)\), ionized calcium \((p = 0.003)\) and
aldosterone \((p = 0.028)\) compared to the healthy controls,
while a statistically significant lower level in the study group
was for phosphorus \((p = 0.003)\) and vitamin D \((p = 0.04)\). Also, among patients with hyperparathyroidism, a strong positive correlation between aldosterone and PTH was
demonstrated \((r = 0.509, p < 0.05)\), while no correlation be-
tween aldosterone and PTH was found among subjects with
normal PTH concentration \((p = -0.285, p > 0.05)\). The most valuable finding in this study was the independent association
of aldosterone and PTH \((\beta = 2.710; p = 0.011)\).

These data imply that there is a possible association
between the PTH and RAA system in patients with primary hy-
perparathyroidism. Earlier studies indicated that activation
of the RAA system is associated with high circulating PTH
concentrations. In a cross-sectional study of 192 hyper-
tensive patients, patients with primary aldosteronism had
higher plasma PTH concentrations than patients with essential hypertension [30]. The molecular background as a possible link between the various components of PTH and RAAS has not yet been sufficiently studied, but an increasing number of studies suggest that there is a bidirectional association between aldosterone and PTH. It is known that cells of the parathyroid gland possess the mineralocorticoid receptor and the PTH receptor type I is present in the adrenal gland [31]. The effect of PTH on the concentration of aldosterone in the plasma may be direct or indirect, related to the concentration of the renin in the plasma [32]. PTH has been shown to increase aldosterone production from adrenocortical cells and to affect angiotensin II-induced adrenal aldosterone secretion [32, 33], which is in concordance

| Variables          | Study group PHPT (N = 48) | Control group (N = 30) | p   |
|--------------------|---------------------------|------------------------|-----|
| Age (years)        | 66 (52–72)                | 61 (54–68)             | NS  |
| Female (n/N) (%)   | 40 (83.3)                 | 24 (80.0)              | NS  |
| Kidney stones (n/N)| 12 (25.0)                 | 3 (10.0)               | 0.001|
| Osteoporosis (n/N) | 14 (29.2)                 | 4 (13.3)               | 0.004|
| Hypertension (n/N) | 28 (58.3)                 | 9 (30.0)               | 0.028|
| ACE inhibitors (n/N) | 10 (35.7)            | 4 (44.4)               | NS  |
| Diuretics (n/N) (%)| 9 (32.1)                  | 3 (33.3)               | NS  |
| Beta blockers (n/N) | 11 (39.3)                | 4 (44.4)               | NS  |

Normally distributed variables presented as x ± SD and skewed variables by median (interquartile range); categorical variables presented as n (%); NS—not significant; PHPT—Primary hyperparathyroidism; ACE—angiotensin converting enzyme.

| Variables          | Study group PHPT (N = 48) | Control group (N = 30) | p   |
|--------------------|---------------------------|------------------------|-----|
| Renin (pg/ml)      | 9.49 (5.1–18.6)           | 7.82 (4.5–11.3)        | NS  |
| Aldosterone (pg/ml)| 126.59 ± 58.07            | 96.37 ± 58.17          | 0.028|
| Aldosterone/renin ratio | 11.17 (5.97–22.3) | 11.48 (7.96–17.12) | NS  |
| PTH (pg/ml)        | 159.5 (120.9–263)         | 74 (65–92.70)          | ≤0.001|
| Calcium (mmol/l)   | 2.72 ± 0.39               | 2.52 ± 0.17            | 0.010|
| Ca++ (mmol/l)      | 1.27 ± 0.19               | 1.15 ± 0.09            | 0.003|
| Phosphorus (mmol/l)| 0.82 ± 0.20               | 0.95 ± 0.18            | 0.003|
| 25 (OH) D (nmol/l)| 48.86 ± 22.54             | 62.45 ± 23.75          | 0.040|

Normally distributed variables presented as x ± SD and skewed variables by median (interquartile range); NS—not significant; PHPT—Primary hyperparathyroidism; Ca++—ionized calcium.

**Figure 1:** Correlation between PTH and renin in the study group \( (r = 0.688, p < 0.05) \).
with our data showing a strong positive correlation between PTH and renin as well as with aldosterone. A research team of Mazzocchi et al. documented that both PTH and parathyroid hormone-like peptide-PTHrP stimulate aldosterone secretion in the zona glomerulosa of the adrenal gland by binding to PTH/PTH-rP receptors and activating the adenylate cyclase/protein kinase C cascade as well as phospholipase C/protein kinase C dependent signaling cascade in a dose dependent manner [34]. Although we did not provide experimental data, our finding of that PTH is the strongest predictive variable of aldosterone secretion supports previous study results. Previous results from clinical studies indicate the same direction as our research. In the study by Brown et al., it was observed that patients with the highest PTH values were those who had high serum aldosterone and low renin activity (the “primary aldosteronism” phenotype). On the other hand, patients with the secondary aldosteronism phenotype (high renin activity and high aldosterone) had a PTH level that did not differ from subjects with low or normal aldosterone levels, suggesting that the phenotype of hyperaldosteronism and chronically elevated aldosterone may affect PTH elevation [27]. These results are in concordance with another study in patients with PA that had a significant increase of PTH, pointing on the bidirectional link between zona glomerulosa of the adrenal gland and parathyroid gland [35]. In a study by Brunaud et al., it was shown that aldosterone concentrations in patients with primary hyperparathyroidism before surgery correlated positively with PTH levels in these patients [32]. There are some conflicting studies evaluating the correlation between aldosterone and PTH levels in hypertensive patients, before and after parathyroidectomy, without alteration of the RAAS after surgery [36]. In another study, the authors concluded that patients with high levels of PTH after parathyroidectomy have a more severe disease [37]. Therefore, from future studies evaluating the impact of parathyroidectomy in symptomatic and asymptomatic patients with primary hyperparathyroidism, we will gain more

| Variables | Study group PHPT (N=48) | Control group (N=30) |
|-----------|-------------------------|----------------------|
| Renin (pg/ml) | PTH (pg/ml) | Total calcium (mmol/l) | Ionized calcium (mmol/l) | PTH (pg/ml) | Total calcium (mmol/l) | Ionized calcium (mmol/l) |
| | r | p | r | p | r | p | r | p |
| Renin (pg/ml) | 0.688 | <0.05 | 0.673 | <0.05 | 0.641 | <0.05 |
| Aldosterone (pg/ml) | 0.509 | <0.05 | 0.189 | >0.05 | 0.166 | >0.05 |
| Renin (pg/ml) | -0.383 | >0.05 | -0.060 | >0.05 | -0.118 | >0.05 |
| Aldosterone (pg/ml) | -0.285 | >0.05 | -0.200 | >0.05 | -0.313 | >0.05 |

Legend: PTH – Parathyroid hormone; PHPT-Primary hyperparathyroidism
knowledge whether surgery decreased risk of cardiovascular mortality in all patients in the PHPT group.

Our results showed a strong positive correlation between PTH and renin concentration in patients with primary hyperparathyroidism. These data are in concordance with the results of the studies suggesting that PTH may be a direct or indirect stimulator of plasma renin activity. Grant et al., in order to examine the effect of PTH on renin secretion, gave patients an infusion of a parathyroid hormone-like peptide, which resulted in increased aldosterone secretion and tetrahydroaldosterone excretion but also an increase in plasma renin concentration [38]. This direct stimulation of PTH on renin secretion is possible since PTH has a direct effect on juxtaglomerular cells because PTH receptors are detected on isolated glomerular blood vessels [39].

Our study showed a strong positive correlation between total and ionized calcium and renin, but this type of relationship was absent between Ca and aldosterone in patients with hyperparathyroidism. A number of studies have shown that conditions with chronically elevated ionized calcium concentrations or with activation of calcium-sensitive receptors are associated with increased plasma renin activity [31, 40]. These data point to another, indirect mechanism of renin increase caused by chronic hypercalcemia. Also, that supports the theory of indirect stimulation of aldosterone by PTH via renin release. Atchison et al. showed that the chronic hypercalcemia can indirectly reduce the level of aldosterone by weakening the response to angiotensin II [40].

Elevated circulating PTH is considered as an independent risk factor for cardiovascular events and mortality [10, 41]. Fisher et al. documented that PHPT is associated with a higher rate of hypertension [42]. Also, cardiovascular morbidity and mortality have been shown to be increased in patients with elevated plasma aldosterone concentrations [43]. An interplay between PTH and aldosterone can increase cardiovascular risk and can adversely affect the various cardiovascular diseases [44]. In primary hyperparathyroidism, an increased risk of developing the cardiovascular disease may exist due to increased activity of the RAA system. Thus, in patients with hyperparathyroidism, who have in adenomatous altered tissue increase in the expression of type 1 angiotensin II receptors, the concomitant hyperaldosteronism can aggravate arterial stiffness, endothelial dysfunction, blood pressure elevation, cardiac hypertrophy and cardiovascular disease [11, 12]. In our study, statistically significantly more patients had a hypertension than subjects of matched sex and age in a control group which supports previous data.

On the other hand, in a large retrospective study including normotensive PHPT patients, Castellano et al. did not find a significant correlation between aldosterone and PTH [45]. These results are suggesting that in RAAS activation in PHPT patients, a positive correlation can be found between aldosterone levels and PTH, rather than in a normotensive state.

Taking into account all these data, one can also hypothesized that detecting the level of aldosterone is necessarily in primary hyperparathyroidism in order to spot and treat the disorder in time.

A large number of studies support clinically relevant interactions between parathyroid hormone and aldosterone, as our research has shown. It has been suggested that treatment of primary hyperparathyroidism, may have a positive effect on the cardiovascular system, reducing the activity of PTH and consequently aldosterone [31].

5. Conclusion

An independent relationship between parathyroid hormone and aldosterone in patients with primary hyperparathyroidism and the correlation between renin and PTH as well as with calcium indicate not only the direct but also the indirect associations between PTH and aldosterone in primary hyperparathyroidism. These findings may represent another possible mode of RAAS-induced organ damage and should help in finding appropriate diagnostic methods to estimate a cardiovascular risk and an adequate treatment to prevent cardiovascular disease in primary hyperparathyroidism.

Abbreviations

| Acronym | Description |
|---------|-------------|
| PTH     | Parathyroid hormone |
| Ca²⁺    | Ionized calcium |
| CaSR    | Calcium-sensitive receptor |
| FGF-23  | Fibroblast growth factor 23 |
| pHPT    | Primary hyperparathyroidism |
| RAAS    | Renin-angiotensin-aldosterone system |
| ATR1    | Angiotensin type 1 receptors |
| ATR2    | Angiotensin type 2 receptors |
| PA      | Primary hyperaldosteronism |
| ACE     | Angiotensin converting enzyme |

Data Availability

The data used to support the results of our study are shown within the article.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

References

[1] M. F. Holick, S. M. Krane, J. T. Potts, G. H. Williams, and R. G. Dluhy, "Endocrinology and metabolism," Harrison’s Principles of Internal Medicine, The McGraw-Hill Medical Publishing Division, New York, NY, USA, 16th edition, 2005.
[2] R. Mihail and J. R. Farndon, "Parathyroid disease and calcium metabolism," British Journal of Anaesthesia, vol. 85, no. 1, pp. 29–43, 2000.
[3] J. P. Bilezikian, N. E. Cusano, A. A. Khan, J.-M. Liu, C. Marcocci, and F. Bandeira, "Primary hyperparathyroidism," Nature Reviews Disease Primers, vol. 2, Article ID 16033, 2016.
[4] A. J. Felsenfeld, M. Rodriguez, and E. Aguilera-Tejero, "Dynamics of parathyroid hormone secretion in health and secondary hyperparathyroidism," Clinical Journal of the American Society of Nephrology, vol. 2, no. 6, pp. 1283–1305, 2007.
[39] P. C. Churchill, “Second messengers in renin secretion,” *American Journal of Physiology*, vol. 249, pp. F175–F184, 1985.

[40] D. K. Atchison and W. H. Beierwaltes, “The influence of extracellular and intracellular calcium on the secretion of renin,” *Pflügers Archiv*, vol. 465, no. 1, pp. 59–69, 2013.

[41] A. Heyliger, V. Tangpricha, C. Weber, and J. Sharma, “Parathyroidectomy decreases systolic and diastolic blood pressure in hypertensive patients with primary hyperparathyroidism,” *Surgery*, vol. 146, pp. 1042–1047, 2009.

[42] S. B. Fisher and N. D. Perrier, “Primary hyperparathyroidism and hypertension,” *Gland Surgery*, vol. 9, no. 1, pp. 142–149, 2020.

[43] B. J. He and M. E. Anderson, “Aldosterone and cardiovascular disease: the heart of the matter,” *Trends in Endocrinology and Metabolism*, vol. 24, no. 1, pp. 21–30, 2013.

[44] V. Naik, “Aldosterone and parathyroid hormone: evidence for a clinically relevant relationship,” *The Journal of Clinical Endocrinology and Metabolism*, vol. 4, no. 3, pp. 1–4, 2019.

[45] E. Castellano, M. Pellegrino, V. Tardivo, R. Attanasio, A. Boriano, and G. Borretta, “Aldosterone secretion in patients with primary hyperparathyroidism without arterial hypertension,” *Endocrine Practice*, vol. 27, no. 11, pp. 1072–1076, 2021.