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Review Article

Association of serum parathyrine and calcium levels with primary aldosteronism: a meta-analysis

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Abstract: Primary aldosteronism (PA) represents major cause of secondary hypertension, strongly associated with high cardiovascular morbidity and mortality. Aldosterone excess may influence mineral homeostasis, through higher urinary calcium (Ca) excretion reducing calcium plasma levels and leading to secondary increase of parathyrine (PTH). The purpose of the present study is to clarify the association of serum PTH and Ca levels with PA using a meta-analysis approach. We searched articles indexed in the PubMed, OVID and Sciencedirect published as of September 2014 that met our predefined criteria. Six articles with 748 subjects from 8 case-control studies were identified. Overall, pooled analysis indicated that subjects with PA had higher serum PTH concentrations and lower Ca levels than controls with essential hypertension (EH) (PTH: SMD = 1.146, 95% CI = [0.774, 1.518]; Ca: SMD = -0.698, 95% CI = [-1.102,-0.294]). Further subgroup analysis stratified by geological location found a similar pattern both in Italy and Austria (Italy: for PTH, SMD = 1.176, 95% CI = [0.758, 1.593], for Ca, SMD = -0.669, 95% CI = [-1.119,-0.219]; Austria: for PTH, SMD = 1.004, 95% CI = [0.359, 1.648], for Ca, SMD = -0.900, 95% CI = [-1.543,-0.257]). In addition, the subgroup analysis stratified by type of Ca measurement also found a similar pattern by spectrophotometry (SMD = -1.078, 95% CI = [-1.532, -0.623]), but not by ion selective electrode (SMD = -0.248, 95% CI = [-0.810, 0.315]). Sensitivity analysis showed that excluding any one study from the pooled analysis did not vary the results substantially. No evidence of publication bias was observed. In conclusion, this meta-analysis supports a significant association of PTH and Ca concentration with PA. Therefore, the high levels of PTH and low Ca concentrations in serum can be used as a variable predictor for PA.

Keywords: Parathyrine, calcium, primary aldosteronism, meta-analysis

Introduction

Primary aldosteronism (PA) is a condition caused by over production of aldosterone and is the most common endocrine cause of secondary arterial hypertension accounting for 0.5-13% of all hypertensive subjects [1]. In a large prospective study of 1180 patients with newly diagnosed arterial hypertension, primary aldosteronism was diagnosed in 11% of patients [2]. Patients with PA typically present with hypertension, high plasma aldosterone concentrations that are typically associated with a low plasma rennin activity levels, and varying degrees of hypokaliemia and metabolic alkalosis. Besides cardiovascular and metabolic alterations, experimental studies in rats showed that aldosterone excess may also impact on mineral homeostasis [3]. Alterations of calcium metabolism and parathyroid function, namely reduced concentration of serum calcium (Ca) and elevated circulating level of parathyrine (PTH) which is considered well-known effects on bone and calcium metabolism, have been reported in PA [4, 5]. In particular, hyperaldosteronism is reported to elevate urinary calcium excretion with the consequent trend towards a decrease of serum Ca, which can determine secondary increase of PTH [6, 7]. Some clinical studies found that there was a significant relationship between PTH, Ca status with PA. It was reported that patients with PA had higher PTH levels and lower Ca concentrations than controls with essential hypertension (EH) [8-12]. However, there was no correlation between serum Ca levels and PA in a study firstly conducted in humans, although patients with PA were detected to have significantly higher concentrations of PTH compared to both normal and hypertensive subjects [13].

Published investigations on the association of serum PTH and Ca concentrations with PA have yielded inconclusive results. Therefore, we performed a comprehensive and critical meta-analysis of the studies, in order to draw a clearer and evidence-based conclusion on the association of PTH and Ca levels with PA.

Materials and methods

Search strategy

We searched the medical literature published in English in the PubMed, OVID and Sciencedirect up to September 2014. Literature searches were performed using medical subject heading (MeSH) or free text words. The searching keywords were: [parathyrine OR calcium] AND [primary aldosteronism]. Emails were sent to the authors of identified studies for additional information if necessary. Reference lists of all eligible studies were screened to identify potentially eligible studies.

Selection criteria

Two authors (Yiyun Zhang and Bo Feng) conducted the search independently. Titles and abstracts were screened for subject relevance. Studies that could not be definitely excluded based on abstract information were also selected for full text screening. Two authors (Yiyun Zhang and Bo Feng) independently selected eligible studies for inclusion possibility. Where there was a disagreement for study inclusion, a discussion was held to reach a consensus.

Eligible studies should meet the following criteria: (1) human study; (2) case-control study or cohort study or randomized clinical trial; (3) subjects with no other diseases and no drugs intake which might influence the serum levels of PTH or Ca; (4) studies providing data of serum PTH or Ca levels for both subjects with PA and controls with EH; (5) the two groups were well matched for age, sex, systolic blood pressure (SBP) and diastolic blood pressure (DBP).

Exclusion criteria included: (1) in vitro or laboratory study; (2) animal study; (3) review or case report; (4) subjects with diseases and drugs intake which might influence the serum levels of PTH or Ca; (5) studies not providing serum PTH or Ca levels for either subjects with PA or controls with EH.

Data extraction and quality assessment

Two authors (Yiyun Zhang and Bo Feng) independently extracted data using a standard form. The following information was extracted from each included study: type of study, country, first author's family name, and year of publication, demography of subjects (number of patients, age and sex), and type of PTH or Ca measurement, data on serum levels of SBP, DBP, PTH and Ca.

The qualities of all included studies were assessed using the Newcastle-Ottawa Scale (NOS). The assessment tool focused on three aspects, including participant selection, comparability and exposure. The studies would be assigned stars of 9 if all items were satisfied. Two authors (Yiyun Zhang and Bo Feng) assessed the quality independently.

Statistical analysis

The extracted data were used to perform meta-analysis to obtain the standardized mean difference (SMD) and 95% confidence intervals (CI). The SMDs were calculated using either fixed-effects models or, in the presence of heterogeneity, random-effects models. Heterogeneity between studies was tested through the Chi-square and I-square tests. If the I^2 value was greater than 50% and the p value was less than 0.05, the meta-analysis was considered as homogeneous.

Subgroup analyses were used to identify associations between PTH or Ca levels and other relevant study characteristics as possible sources of heterogeneity. The stability of the study was also detected by sensitivity analysis, through re-meta-analysis with one involved study excluded each time. Publication bias was measured using Begg's tests, Egger's test and visualization of funnel plots. All statistical analyses were performed with Stata version 11.0 (StataCorp, College Station, TX).

Results

Literature search

The literature search identified a total of 421 primary articles. These articles were included for full-text assessment, of which 415 were excluded for one of the following reasons: (1)

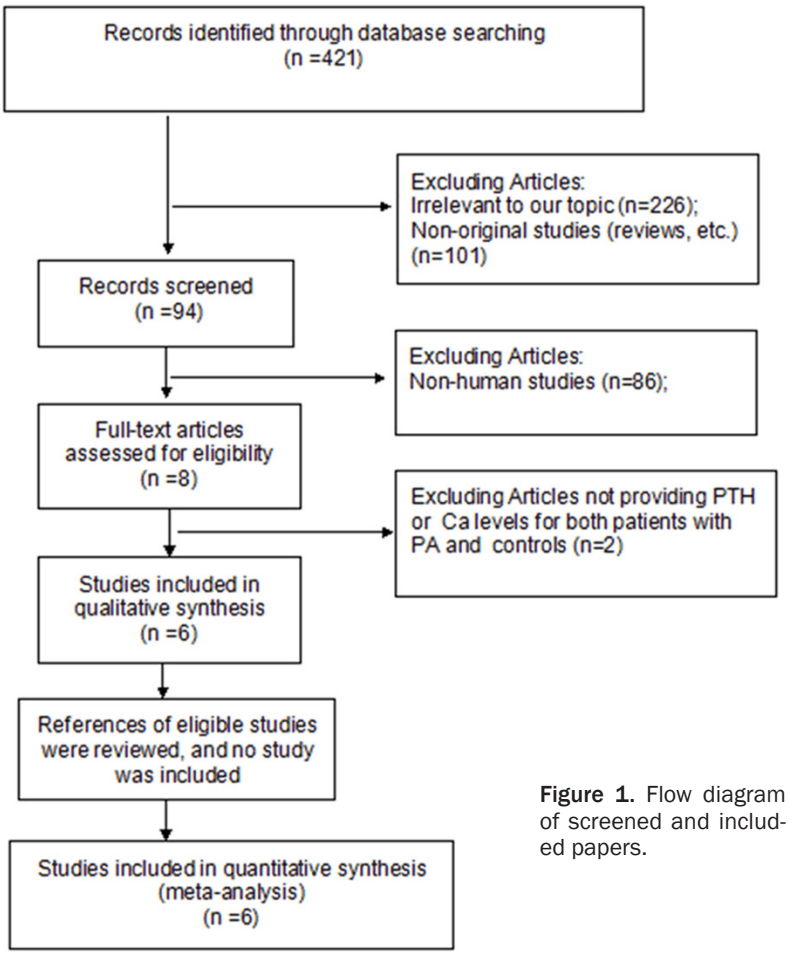

Figure 1. Flow diagram of screened and included papers.

irrelevant to our topic (n = 226), (2) non-original studies (reviews, etc.) (n = 101), (3) non-human studies (n = 86), (4) articles not providing PTH or Ca levels for both subjects with PA and EH controls (n = 2). Overall, six eligible articles with 748 subjects from 8 case-control studies were considered in the analysis [8-13]. A flow diagram of the study selection process is presented in **Figure 1**.

Study characteristics and quality assessment

The detailed characteristics of the included studies and the results of the quality assessment were summarized in **Tables 1**, **2**. The earliest study was published in 1995, and the latest in 2014. By geographic location, studies were conducted in 2 different countries (Italy and Austria). The number of subjects in each study ranged from 20 to 226. Four articles with 6 case-control studies measured the PTH by radiometric assay, while 2 article with 2 case-control studies by electrochemiluminescence immunoassay. Three articles with 4 case-control studies measured the Ca by ion selective electrode, the other 3 article with 4 case-control studies by spectrophotometry. Of note, all the eligible articles assess both the PTH and Ca levels, and were included in both two groups. The overall study quality averaged 6.9 stars (range, 6-7) on a scale of 0 to 9.

PTH levels and primary aldosteronism

The random-effects meta-analysis results indicated that subjects with PA had higher serum PTH levels than EH controls (SMD = -1.146, 95% CI = [0.774, 1.518]). The 8 sets of results showed a statistically significant amount of heterogeneity (I^2 = 76.3%, P < 0.001) (**Figure 2**).

The subgroup analysis showed that the type of PTH measurement had influence on the levels of PTH in patients with PA and EH controls. We found that the subjects with PA had higher PTH than EH controls in different countries (Italy: SMD = 1.176, 95% CI = [0.758, 1.593]; Austria: SMD = 1.004, 95% CI = [0.359, 1.648]). Further subgroup analysis stratified by different type of PTH measurement found that the subgroup analysis stratified by type of PTH measurement found there was no significant heterogeneity among the studies which measured the PTH levels by electrochemiluminescence immunoassay (I^2 = 0, P < 0.001). Summary of further subgroup analysis of the related study arms is given in **Table 3**.

Ca levels and primary aldosteronism

The random-effects meta-analysis results indicated that subjects with PA had lower serum Ca levels than EH controls (SMD = -0.698, 95% CI = [-1.102, -0.294]). The 8 sets of results showed a statistically significant amount of heterogeneity (I^2 = 82.0%, P < 0.001) (**Figure 3**).

Table 1. Characteristics of subjects in eligible studies (for PTH)

Studies	Country	Type of PTH measurement	Sex	Primary aldosteronism				Control (essential hypertension)				Score
				SBP/DBP (mm Hg) (mean ± SD)	Age	N	PTH concentration (mean ± SD)	SBP/DBP (mm Hg) (mean ± SD)	Age	N	PTH concentration (mean ± SD)	
Rossi 1995	Italy	Radiometric assay	Both	168.4±15.8/102.7± 2.5	52.4±12.9	10	70±24 pg/ml	164.5±13.1/103.4±4.6	46.4±5.1	10	36±10 pg/ml	6
Rossi 1998	Italy	Radiometric assay	Both	161±3/105±1	31~71	16	47.5±5.1 pg/ml	157±3/102±1	33~69	16	33.4±3.5 pg/ml	7
Pilz 2012	Austria	Electrochemiluminescence immunoassay	Both	149±23/96±13	50.2±15.7	10	67.8±26.9 pg/ml	154±23/94±13	50.1±17	182	46.5±20.9 pg/ml	7
Rossi 2012 (1)	Italy	Radiometric assay	Both	155±17/94±10	51±13	46	113.4±45.7 ng/l	149±16/93±15	50±14	74	79±30.8 ng/l	7
Rossi 2012 (2)	Italy	Radiometric assay	Both	155±33/92±19	45±10	12	81.7±29.9 pg/ml	149±16/93±15	50±14	74	79±30.8 ng/l	7
Ceccoli 2013	Italy	electrochemiluminescence immunoassay	Both	158±19/97±11.2	51.6±11	116	82.2±33 pg/ml	151±15/93±7.5	55±10	110	56.4±16.4 pg/ml	7
Petramala 2014 (1)	Italy	Radiometric assay	Both	138.8±19.1/88.3± 9.6	52.8±11.5	35	46±20.1 pg/ml	131±18.8/82.4±12.2	55.6±12.4	73	30.7±11.9 pg/ml	7
Petramala 2014 (2)	Italy	Radiometric assay	Both	137.3±14.5/83.4±9.6	52.5±11.2	38	50.6±20.2 pg/ml	131±18.8/82.4±12.2	55.6±12.4	73	30.7±11.9 pg/ml	7

Table 2. Characteristics of subjects in eligible studies (for Ca)

Studies	Country	Type of Ca measurement	Sex	Primary aldosteronism				Control (essential hypertension)				Score
				SBP/DBP (mm Hg) (mean ± SD)	Age	N	Ca concentration (mean ± SD)	SBP/DBP (mm Hg) (mean ± SD)	Age	N	Ca concentration (mean± SD)	
Rossi 1995	Italy	Ion selective electrode	Both	168.4±15.8/102.7± 2.5	52.4±12.9	10	8.94±0.31 mg/dl	164.5±13.1/103.4± 4.6	46.4±5.1	10	8.93±0.54mg/ml	6
Rossi 1998	Italy	Ion selective electrode	Both	161±3 /105±1	31~71	16	1.23±0.01 mg/dl	157±3/102±1	33~69	16	1.24±0.01mg/ml	7
Pilz 2012	Austria	Spectrophotometry	Both	149±23/96±13	50.2±15.7	10	2.26±0.1 mmol/l	154±23/94±13	50.1±17	182	2.35±0.1 mmol/l	7
Rossi 2012 (1)	Italy	Ion selective electrode	Both	155±17/94±10	51±13	46	2.3±0. 1 mmol/l	149±16/93±15	50±14	74	2.34±0.09 mmol/l	7
Rossi 2012 (2)	Italy	Ion selective electrode	Both	155±33/92±19	45±10	12	2.38±0. 11mmol/l	149±16/93±15	50±14	74	2.34±0.09 mmol/l	7
Ceccoli 2013	Italy	Spectrophotometry	Both	158±19/ 97±11.2	51.6±11	116	8.9±0.3 mEq/l	151±15/ 93±7.5	55±10	110	9.2±0.6 mEq/l	7
Petramala 2014 (1)	Italy	Spectrophotometry	Both	138.8±19.1/88.3± 9.6	52.8±11.5	35	9.2±0.5 mg/dl	131±18.8/82.4±12.2	55.6±12.4	73	9.7±0.3 mg/dl	7
Petramala 2014 (2)	Italy	Spectrophotometry	Both	137.3±14.5/83.4± 9.6	52.5±11.2	38	9.2±0.4 mg/dl	131±18.8/82.4±12.2	55.6±12.4	73	9.7±0.3 mg/dl	7

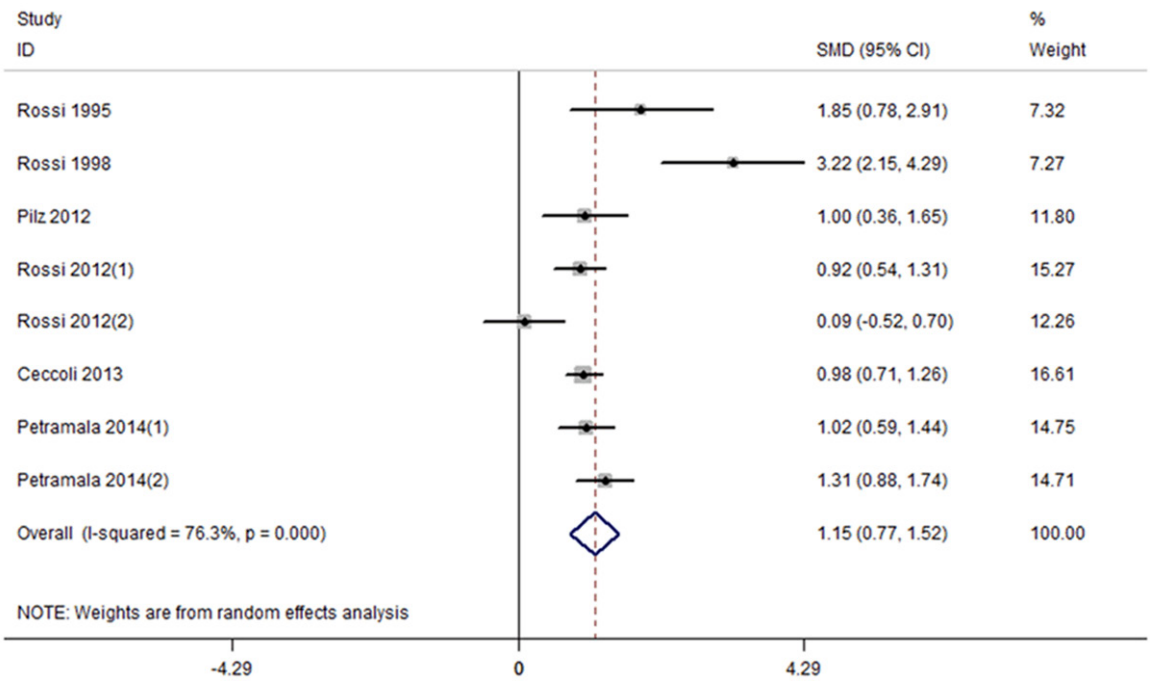

Figure 2. Forest plot of studies in PTH levels for subjects with PA versus EH controls. The combined SMD and 95% confidence intervals (CIs) were calculated using the random-effects model.

Table 3. Differences between studies by subgroup analysis

Subgroups	No. of case-control studies	SMD (95% CI)	I^2 (%)	*p*
PTH levels				
Geographical Location				
Italy	7	1.176 (0.758, 1.593)	79.7	< 0.001
Austria	1	1.004 (0.359, 1.648)	NA	0.002
Type of PTH measurement				
Electrochemiluminescence immunoassay	2	1.146 (0.774, 1.518)	0	< 0.001
Radiometric assay	6	1.263 (0.704, 1.822)	83.0	< 0.001
Ca levels				
Geographical Location				
Italy	7	-0.669 (-1.119, -0.219)	84.4	0.004
Austria	1	-0.900 (-1.543, -0.257)	NA	0.006
Type of Ca measurement				
Ion selective electrode	4	-0.248 (-0.810, 0.315)	69.6	0.388
Spectrophotometry	4	-1.078 (-1.532, -0.623)	78.2	< 0.001

The subgroup analysis showed that the type of Ca measurement had influence on the levels of Ca in patients with PA and EH controls. We found that the subjects with PA had lower serum Ca levels than EH controls both in Italy and Austria (Italy: SMD = -0.669, 95% CI = [-1.119, -0.219]; Austria: SMD = -0.900, 95% CI = [-1.543, -0.257]). Further subgroup analysis stratified by different type of Ca measurement found a similar pattern by spectrophotometry (SMD = -1.078, 95% CI = [-1.532, -0.623]), but not by ion selective electrode (SMD = -0.248, 95% CI = [-0.810, 0.315]). Summary of further subgroup analysis of the related study arms is given in **Table 3**.

Publication bias and sensitivity analysis

Publication bias was determined by Begg's test, Egger's test and visualization of funnel

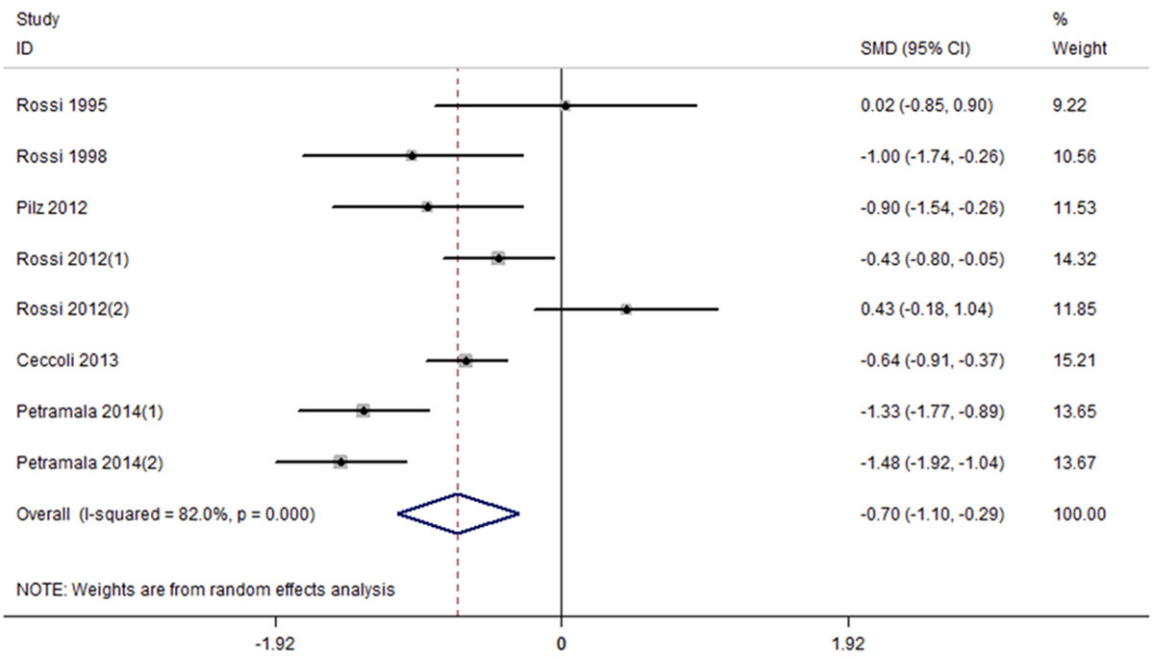

Figure 3. Forest plot of studies in Ca levels for subjects with PA versus EH controls. The combined SMD and 95% confidence intervals (CIs) were calculated using the random-effects model.

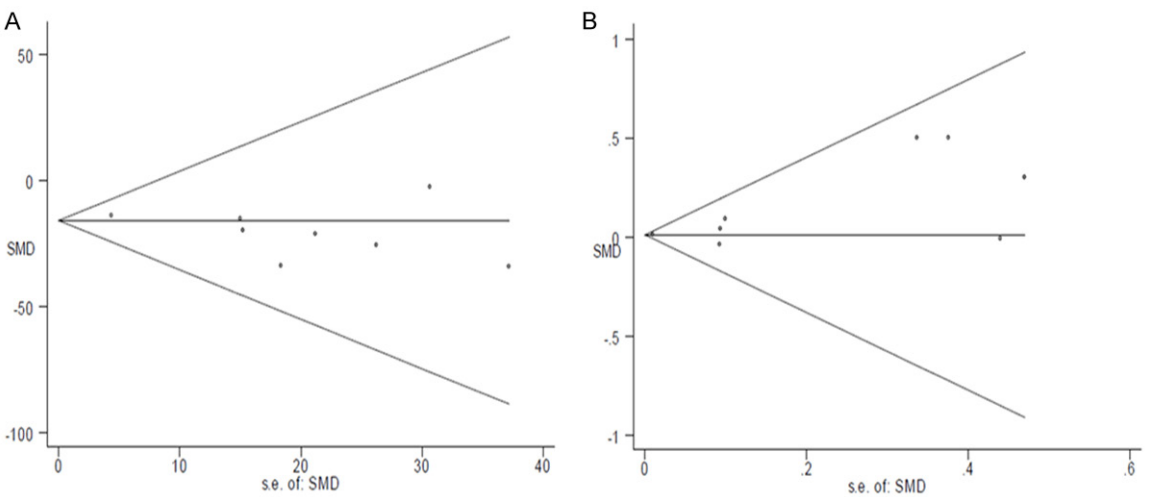

Figure 4. Funnel plot for studies in PTH, Ca levels for subjects with PA versus EH controls. (A) for PTH; (B) for Ca.

plot. There was no evidence of publication bias (PTH: Begg's P = 0.266, Egger's P = 0.266; Ca: Begg's P = 0.174, Egger's P = 0.075) (**Figure 4**). Sensitivity analysis showed that excluding any one study from the pooled analysis did not vary the results substantially (**Table 4**).

Discussion

In the present meta-analysis, the association of serum PTH and Ca levels with PA was examined. Combining the results from 6 articles with 8 case-control studies, it clearly demonstrated that PA patients had higher serum PTH levels than EH controls (SMD = -1.605, 95% CI = [-2.114, -1.096]). In-vitro studies consistently showed that PTH concentration dependently increases aldosterone and cortisol secretion from isolated bovine and human dispersed adrenocortical cells [14, 15]. Moreover, it was shown to enhance the secretagogue effect of angiotensin II on aldosterone [16]. The PTH-related peptide (PTH-rP), a mediator of cancer

Table 4. The heterogeneity of the included studies through sensitivity analysis

Excluded study arm	SMD (95% CI)	I^2 (%)	*p* value
PTH			
Before excluding	1.146 (0.774, 1.518)	76.3	< 0.001
Rossi 1995	1.089 (0.706, 1.472)	78.0	< 0.001
Rossi 1998	0.976 (0.710, 1.242)	54.2	< 0.001
Pilz 2012	1.176 (0.758, 1.593)	79.7	< 0.001
Rossi 2012 (1)	1.207 (0.758, 1.657)	79.5	< 0.001
Rossi 2012 (2)	1.260 (0.915, 1.605)	69.4	< 0.001
Ceccoli 2013	1.212 (0.731, 1.693)	79.6	< 0.001
Petramala 2014 (1)	1.188 (0.744, 1.632)	79.7	< 0.001
Petramala 2014 (2)	1.133 (0.703, 1.563)	78.4	< 0.001
Ca			
Before excluding	-0.698 (-1.102, -0.294)	82.0	0.001
Rossi 1995	-0.772 (-1.193, -0.350)	83.2	<0.001
Rossi 1998	-0.660 (-1.102,-0.218)	84.3	0.003
Pilz 2012	-0.669 (-1.119, -0.219)	84.4	0.004
Rossi 2012 (1)	-0.738 (-1.209, -0.268)	83.1	0.002
Rossi 2012 (2)	-0.856 (-1.215, -0.497)	74.8	<0.001
Ceccoli 2013	-0.699 (-1.217, -0.181)	84.2	0.008
Petramala 2014 (1)	-0.600 (-1.026, -0.173)	80.6	0.006
Petramala 2014 (2)	-0.579 (-0.972, -0.185)	77.0	0.004

hypercalcemia that also acts on type 1 PTH receptor, was also reported to exert a similar effect and to induce proliferation in human adrenocortical carcinoma cells [15, 17, 18]. Furthermore, infusion of aldosterone in rats caused an increase of PTH, thus suggesting a cause-effect relationship between hyperaldosteronism and hyperparathyroidism [19]. Recently, in a relative cohort of patients with unequivocally confirmed PA, Maniero et al. [5] showed a highly significant 31% increase in the number of cases of hyperparathyroidism, thus suggesting that there is a bidirectional functional link between the adrenocortical zona glomerulosa and the parathyroid gland. Moreover, these researchers demonstrated the expression of the mineral corticoid receptors (MR) in both PTH secreting adenoma and in parathyroid tissue, and the MR was predominantly located in the nucleus of the parathyroid cells, indicating that aldosterone participate in a "tonic" regulation of PTH synthesis and secretion [20, 21]. Finally, Tomaschitz et al. [22] showed that patients with PA are with secondary hyperparathyroidism that can be successfully treated with either mineral corticoid. Hence, these findings altogether suggest that PTH could play a role in human primary aldosteronism by triggering and/or maintaining aldosterone secretion and stimulating adrenocortical cell proliferation.

The present study also indicated that PA patients had lower Ca concentrations than EH controls (SMD = -1.605, 95% CI = [-2.114, -1.096]). Aldosterone excess may impact on mineral homeostasis, it indeed increases renal and fecal loss of calcium and reduces calcium plasma levels, leading to secondary increase of parathyroid hormone (PTH) which is, beyond its well-known effects on bone and calcium metabolism, also considered a cardiovascular risk factor [6, 23]. The proposed pathogenetic mechanism for bone involvement in the presence of aldosterone excess seems to be, at least in part, secondary hyperparathyroidism due to an increased urinary excretion of calcium and consequent hypocalcemia. It has been suggested that the increase in aldosterone-mediated renal calcium excretion is the result of decreased proximal tubular reabsorption of sodium and calcium due to extravascular volume expansion, together with a distal reabsorption of sodium but not of calcium [24, 25].

However, our results showed strong heterogeneity among the studies (for PTH: I^2 = 76.3%, P < 0.001; for Ca: I^2 = 82.0%, P < 0.001). Heterogeneity indicates differences in results across the studies. There are two sources of heterogeneity: one is within-study variability which means a difference within a study of estimating the same effect size and it always exists in meta-analysis because of sampling error, the other is between-study variability which means differences among studies in estimating effect size among different population. In present study, the between-study variability was the main source of heterogeneity, because the further subgroup analysis indicated that the sample specimen, type of PTH or Ca measurement was the possible source of heterogeneity. We

found that the subjects with PA had higher PTH and lower Ca levels than EH controls in different countries (Italy and Austria). The subgroup analysis stratified by type of Ca measurement also found a similar pattern by spectrophotometry, but not by ion selective electrode. And the subgroup analysis stratified by type of PTH measurement found there was no significant heterogeneity among the studies which measured the PTH levels by electrochemiluminescence immunoassay ($I^2 = 0$, $P < 0.001$). These findings can well explain that the between-study variability was the main source of heterogeneity.

To the best of our knowledge, this is the first meta-analysis to estimate the association of PTH and Ca levels with PA. We made sure to minimize the bias by means of study procedure. Not only did we search PubMed, OVID and Sciencedirect to identify potential studies, but also we manually examined all reference lists from relevant studies. Sensitivity analysis showed that excluding any one study from the pooled analysis did not vary the results substantially. Publication bias was also absent, as determined by visualization of funnel plot and Begg's test. However, the possible limitations of our study must be considered. First, only 748 subjects from 8 case-control studies and no randomized clinical trial included in the meta-analysis might weaken the quality of the results. In addition, heterogeneity could not be omitted because of methodological diversities between studies, thus the conclusion should be conservative.

In summary, this meta-analysis based random-effect model supports a significant association of PTH and Ca concentration with PA. Therefore, the high levels of PTH and low Ca concentrations in serum can be used as a variable predictor for PA.

Acknowledgements

All authors designed the study together, performed the experiment together, analyzed the data and wrote the paper; all authors approved the final manuscript.

Disclosure of conflict of interest

None.

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