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Bone and mineral metabolism in patients with primary aldosteronism: A systematic review and meta-analysis

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Purpose: Patients with primary aldosteronism (PA) tend to exhibit a high prevalence of osteoporosis (OP) that may vary by whether PA is unilateral or bilateral, and responsive to PA treatment. To explore relationships between bone metabolism, PA subtypes, and treatment outcomes, we performed a systematic review and meta-analysis.

Methods: The PubMed, Embase, and Cochrane databases were searched for clinical studies related to PA and bone metabolism markers. Articles that met the criteria were screened and included in the systematic review; the data were extracted after evaluating their quality. R software (ver. 2022-02-16, Intel Mac OS X 11.6.4) was used for the meta-analysis.

Results: A total of 28 articles were subjected to systematic review, of which 18 were included in the meta-analysis. We found that PA patients evidenced a lower serum calcium level (mean difference [MD] = −0.06 mmol/L, 95% confidence interval [CI]: −0.10 ~ −0.01), a higher urine calcium level (MD = 1.29 mmol/24 h, 95% CI: 0.81 ~ 1.78), and a higher serum parathyroid hormone (PTH) level (MD = 2.16 pmol/L, 95% CI: 1.57 ~ 2.75) than did essential hypertension (EH) subjects. After medical treatment or adrenal surgery, PA patients exhibited a markedly increased serum calcium level (MD = −0.08 mmol/L, 95% CI: −0.11 ~ −0.05), a decreased urine calcium level (MD = 1.72 mmol/24 h, 95% CI: 1.00 ~ 2.44), a decreased serum PTH level (MD = 2.67 pmol/L, 95% CI: 1.73 ~ 3.62), and an increased serum 25-hydroxyvitamin D (25-OHD) level (MD = −6.32 nmol/L, 95% CI: −11.94 ~ −0.70). The meta-analysis showed that the ser um PTH level of unilateral PA patients was significantly higher than that of bilateral PA patients (MD = 0.93 pmol/L, 95% CI: 0.36 ~ 1.49) and the serum 25-OHD lower than that of bilateral PA patients (MD = −4.68 nmol/L, 95% CI: −7.58 ~ 1.77). There were, however, no significant differences between PA and EH patients of 25-OHD, or BMD of femoral neck and lumbar spine. BMDs of the femoral neck or lumbar spine did not change significantly after treatment. The meta-analytical results were confirmed *via* sensitivity and subgroup analyses.

Conclusion: Excess aldosterone was associated with decreased serum calcium, elevated urinary calcium, and elevated PTH levels; these effects may be enhanced by low serum 25-OHD levels. The risks of OP and fracture might be elevated in PA patients, especially unilateral PA patients, but could be reduced after medical treatment or adrenal surgery. In view, however, of the lack of BMD changes, such hypothesis needs to be tested in further studies.

KEYWORDS

primary aldosteronism, osteoporosis, bone metabolism, secondary hyperparathyroidism (secHPT), meta-analysis

Introduction

Osteoporosis (OP) is a common disease characterized by decreased bone mass and strength, and destruction of bone microstructure, increasing the fracture susceptibility. OP can be divided into primary and secondary OP. As secondary OP is considered to be reversible, it is important to identify the cause thereof. Secondary OP can develop in those with diseases of the endocrine and blood systems, and of connective tissue; after drug use; and for many other reasons, of which the use of glucocorticoids (1), (2) is the most common. Recently, the role played by mineralocorticoids in bone metabolism has become recognized; an increasing number of studies have shown that primary aldosteronism (PA) may cause secondary OP (3–5). In PA patients, the adrenal cortex autonomously secretes excessive amounts of aldosterone, resulting in sodium retention and potassium excretion, increased blood volume, and suppression of the activity of the renin-angiotensin-aldosterone system (RAAS). This manifests clinically as hypertension and hypokalemia, and is the most common cause of secondary hypertension. Previous studies have shown that PA can affect bone metabolism, and a bidirectional interaction may be in play between aldosterone and parathyroid hormone (PTH) (6, 7). Hence, this study aimed to explore the relationship between bone metabolism markers and the different subtypes of PA, and the effects of PA treatment through a systematic review and meta-analysis.

Materials and methods

Search strategy

The PubMed, Embase, and Cochrane databases were searched for clinical studies on PA and bone metabolism markers using the term “Hyperaldosteronism” in combination with “PTH, Calcium, BMD, Osteoporosis, and Secondary Hyperparathyroidism”, with restrictions to the English language and human subjects; the databases were searched from their inceptions to March 6, 2022. We additionally searched the Grey Literature database. The above searches followed the PRISMA guidelines. All retrieved papers were imported into Zotero ver. 6.0.

Selection criteria

Inclusion criteria: Randomized controlled trials; cohort, case-control, or observational studies. A PA diagnosis verified by at least one confirmatory test (a captopril challenge; a saline infusion, fludrocortisone suppression, or/and an oral sodium loading test); or *via* adrenal venous sampling (AVS). All studies reported the levels of blood parathyroid hormone (PTH), serum calcium and urinary calcium, serum 25-hydroxy vitamin D (25-OHD), serum alkaline phosphatase (AKP), and bone-specific alkaline phosphatase (BAP); the bone mineral density (BMD); and the prevalence or morbidity from OP, fractures, and hyperparathyroidism (HPT).

Exclusion criteria: The PA diagnosis was unclear or not specified. Clinical data were lacking. The experimental or case group, or cohort, were not PA patients. If PA subtypes were studied, there was no clear explanation as to how the subtypes were diagnosed.

Data extraction and quality assessment

Two researchers independently conducted literature screening and data extraction using a standardized form while operating in a double-blinded manner. We extracted the first author names and countries, type of study, publication year, subject populations, interventions, basic clinical characteristics, bone metabolism markers (biochemical parameters and imaging indices), and follow-up data after PA treatment. The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of case-control and cohort studies. Any disagreement between the two researchers was settled *via* discussion with, or arbitration by, a third specialist.

Statistical analysis

R software (ver. 2022-02-16, Intel Mac OS X 11.6.4) (the "meta" package ver. 5.2-0) was used for statistical analysis. We calculated mean differences (MDs) between patients and controls (with 95% confidence limits [CIs]) for continuous variables, and odds ratios (ORs) with 95% CIs for dichotomous variables. We sought heterogeneity using the I^2 test, and considered that this was absent when $I^2 < 50\%$. If heterogeneity was absent, we used fixed-effect models for meta-analysis, but employed random-effect models when heterogeneity was in play and the causes thereof were not discernible. Publication bias was assessed using the Egger's test; we also drew funnel plots during meta-analyses of at least 10 studies. Visual confirmation of funnel plot symmetry, or an Egger's test P-value > 0.05, indicated no publication bias. We performed sensitivity analysis on only "high quality" studies (NOS scores at least the median of all studies). We also performed subgroup analyses to explore the sources of heterogeneity.

Results

Search results

A total of 494 articles were retrieved, including 270 from PubMed, 215 from Embase, 9 from Cochrane, but none from the Grey Literature (Figure 1). After removing duplicate studies, reading the titles, and screening the full texts, 28 works were finally included in the systematic review (Table 1), of which 13 were newly included compared to a previous study (3). Eighteen articles were included in the meta-analysis. In detail, 12 studies (14, 17, 18, 21, 25–27, 29–33) compared 3,318 PA patients to 11,024 essential hypertension (EH) subjects in terms of the serum calcium and urinary calcium levels; the serum PTH, 25-OHD, and AKP levels; and the BMD. Twelve studies (17), (18), (25), (27, 29–31), (12, 15, 16, 28, 33) compared 501 PA patients before medical or surgical treatment to 491 who were followed-up after treatment in terms of the serum calcium and urinary calcium levels; the serum PTH, 25-OHD, and BAP levels; and the BMD. Eight studies (nine datasets) (14), (25), (26), (29), (15), (11, 13, 19) compared 489 unilateral PA patients with 558 bilateral PA patients (three studies diagnosed PA *via* AVS after ACTH stimulation; four *via* AVS without ACTH stimulation; and one *via* AVS both with and without ACTH stimulation); all presented the serum calcium and urinary calcium and PTH and 25-OHD levels; and the BMD.

Quality assessment

Of the 28 included articles, 26 were case-control studies, one a cohort study, and one a descriptive study. The quality of the case-control studies is shown in Supplementary Table 3; the NOS score of the cohort study was 8. The NOS scores of all studies were at least 6 (median 8).

PA vs. EH

Eight studies reported significantly lower serum calcium levels in PA than EH patients (MD = –0.06 mmol/L, 95% CI: –0.10 ~ –0.01). The urinary calcium level was significantly higher in seven studies that compared PA patients to EH subjects (MD = 1.29 mmol/24 h, 95% CI: 0.81 ~ 1.78). Ten studies found that the serum PTH level was significantly higher in PA patients than in EH subjects (MD = 2.16 pmol/L, 95% CI: 1.57 ~ 2.75). While no significant differences were found between PA and EH patients on 25-OHD, on BMD of femoral neck and lumbar spine and on AKP (Figure 2).

A comparison of data before and after treatment

Nine studies reported significantly higher serum calcium levels (MD = –0.08 mmol/L, 95% CI: –0.11 ~ –0.05) after than before treatment of PA patients. The urinary calcium level was significantly lower after treatment (MD = 1.72 mmol/24 h, 95% CI: 1.00 ~ 2.44) in seven studies; the serum PTH level was significantly lower in 12 studies (MD = 2.67 pmol/L, 95% CI: 1.73 ~ 3.62); and the serum 25-OHD was significantly higher (MD = –6.32 nmol/L, 95% CI: –11.94 ~ –0.70) in nine studies. None of the BAP level or the BMDs of the femoral neck or lumbar spine changed significantly after treatment (Figure 3).

Unilateral vs. bilateral PA

The serum PTH level was significantly higher in unilateral than bilateral PA patients (MD = 0.93 pmol/L, 95% CI: 0.36 ~ 1.49) in eight studies (nine datasets). Six studies found that the serum 25-OHD level was significantly lower in unilateral than bilateral PA patients (MD = –4.68 nmol/L, 95% CI: –7.58 ~ –1.77). However, no significant differences were found in terms of

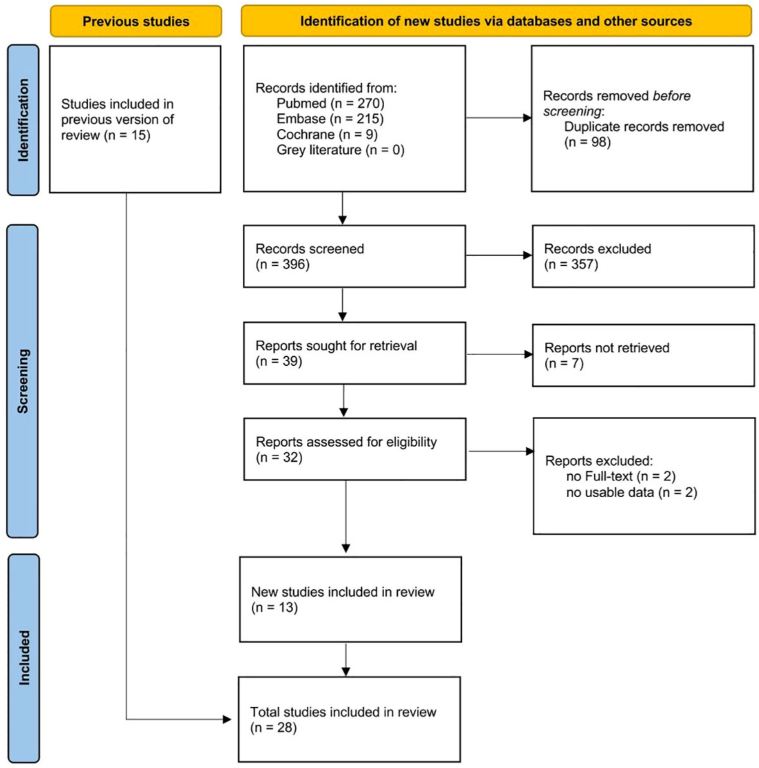

FIGURE 1
Flow diagram of literature selection.

TABLE 1 Characteristic of studies included in systematic review and meta-analysis.

Study	Design	Country	Patient and Control	N	age (year)	Male (%)	NOS scores
Zavatta, 2022 (8)	case-control	Italy	PA NFA	26 39	58.00 ± 8.90 59.00 ± 8.80	11 (42.3%) 17 (43.6%)	8
Tang, 2022 (9)	case-control	China	PA SA(GS+BS)	20 37	38.80 ± 10.10 36.10 ± 14.60	11 (55.0%) 19 (51.4%)	7
Liu, 2021 (10)	case-control	China	PA NFA	356 417	50.00 ± 11.00 51.00 ± 12.00	203 (57.0%) 219 (52.5%)	6
Kometani, 2021 (11)	case-control	Japan	(a) unilateral PA bilateral PA (without ACTH)	60 54	52.00 ± 12.00 52.00 ± 12.00	31 (51.7%) 27 (50.0%)	6
			(b) unilateral PA bilateral PA (with ACTH)	19 105	55.00 ± 11.00 51.00 ± 11.00	12 (63.2%) 52 (49.5%)	
Gravvanis, 2021 (12)	case-control	Greece	PA before treatment PA after treatment	63 63	60.00(31.00,78.00) 60.00(31.00,78.00)	37 (58.7%) 37 (58.7%)	8
Yokomoto, 2020 (13)	case-control	Japan	unilateral PA bilateral PA (with ACTH)	37 76	56.00 ± 14.00 54.00 ± 11.00	25 (67.6%) 23 (30.3%)	7
Tuersun, 2020 (14)	case-control	China	(a) PA EH	156 156	49.86 ± 8.72 48.99 ± 8.60	88 (56.4%) 88 (56.4%)	8
				76 80	49.11 ± 8.38 48.79 ± 8.86	43 (56.6%) 47 (58.8%)	

(Continued)

TABLE 1 Continued

Study	Design	Country	Patient and Control	N	age (year)	Male (%)	NOS scores
			(b) unilateral PA				
			bilateral PA				
			(without ACTH)				
Asbach, 2020 (15)	case-control	German	(a) unilateral PA	70	49.00(43.00,59.00)	44 (62.9%)	8
			bilateral PA	55	45.00(41.00,53.00)	35 (63.6%)	
			(with ACTH)				
			(b) PA before treatment	60	-	38 (63.3%)	
			PA after treatment	60	-	38 (63.3%)	
Adolf, 2020 (16)	case-control	German	(a) PA	36	59.00(53.00,64.00)	0 (0%)	8
			HS	18	54.00(44.00,60.00)	0 (0%)	
			(b) PA before treatment	36	59.00(53.00,64.00)	0 (0%)	
			PA after treatment	36	59.00(53.00,64.00)	0 (0%)	
Lenzini, 2019 (17)	case-control	Italy	(a) PA	42	52.00 ± 11.22	24 (57.1%)	7
			EH	63	52.00 ± 10.00	33 (52.4%)	
			(b) unilateral PA	27	52.00 ± 11.00	15 (55.6%)	
			bilateral PA	15	52.00 ± 12.00	9 (60.0%)	
			(c) PA before treatment	42	52.00 ± 11.22	24 (57.1%)	
			PA after treatment	32	52.00 ± 11.02	-	
Loh, 2018 (18)	case-control	Malaysia	(a) PA	18	50.00(38.00,58.75)	11 (61.1%)	7
			EH	17	50.00(38.50,61.50)	11 (64.7%)	
			(b) PA before treatment	15	-	-	
			PA after treatment	15	-	-	
Lim, 2018 (19)	case-control	Korean	unilateral PA	23	46.50 ± 11.50	9 (39.1%)	8
			bilateral PA	19	51.50 ± 9.80	12 (63.2%)	
			(with ACTH)				
Kim, 2018 (5)	case-control	Korean	PA	72	56.73 ± 8.50	-	8
			AI	335	54.64 ± 9.95	-	
Shu, 2018 (20)	case-control	China	OP	186	59.60 ± 4.35	0 (0%)	8
			OE	96	58.70 ± 4.40	0 (0%)	
			HS	42	58.60 ± 4.90	0 (0%)	
Wu, 2017 (21)	cohort	China	PA	2533	50.55 ± 14.57	1176 (46.4%)	8
			EH	10132	50.69 ± 17.90	4708 (46.5%)	
Salcuni, 2017 (22)	case-control	Italy	(a) PA	12	60.40 ± 13.50	-	9
			non-PA	310	61.10 ± 9.30	-	
			(b) OP	213	-	-	
			HS	109	-	-	
Notsu, 2017 (23)	case-control	Japan	PA	56	58.70 ± 11.10	25 (44.6%)	8
			HS	56	59.40 ± 11.50	25 (44.6%)	
Zhang, 2016 (24)	case-control	China	PA	84	50.00 ± 10.00	44 (52.4%)	6
			NFA	58	55.00 ± 8.00	21 (36.2%)	
Jiang, 2016 (25)	case-control	China	(a) PA	242	49.00(41.00,57.00)	131 (54.1%)	8
			EH	120	50.00(42.00,58.00)	53 (44.2%)	
			(b) unilateral PA	123	46.57 ± 11.33	57 (46.3%)	
			bilateral PA	119	52.70 ± 12.01	74 (62.2%)	
			(without ACTH)				
			(c) PA before treatment	99	-	-	
			PA after treatment	99	-	-	
Petramala, 2014 (26)	case-control	Italy	(a) PA	73	52.50 ± 11.20	-	6
			EH	73	55.60 ± 12.40	-	
			HS	40	55.70 ± 6.10	-	
			(b) unilateral PA	35	52.80 ± 11.50	-	
			bilateral PA	38	52.50 ± 11.20	-	
			(without ACTH)				
Ceccoli, 2013 (27)	case-control	Italy	(a) PA	116	51.60 ± 11.00	65 (56.0%)	7
			EH	110	55.00 ± 10.00	35 (31.8%)	

(Continued)

TABLE 1 Continued

Study	Design	Country	Patient and Control	N	age (year)	Male (%)	NOS scores
			(b) PA before treatment	40	-	-	
			PA after treatment	40	-	-	
Salcuni, 2012 (28)	case-control	Italy	(a) PA	11	56.00 ± 9.30	4 (36.4%)	10
			NFA	15	56.70 ± 9.50	5 (33.3%)	
			(b) PA before treatment	9	-	-	
			PA after treatment	9	-	-	
Rossi, 2012 (29)	case-control	Italy	(a) PA	58	49.76 ± 12.60	-	9
			EH	74	50.00 ± 14.00	-	
			(b) unilateral PA	46	51.00 ± 13.00	-	
			bilateral PA (without ACTH)	12	45.00 ± 10.00	-	
			(c) PA before treatment	46	51.00 ± 13.00	-	
			PA after treatment	46	52.00 ± 12.00	-	
Pilz, 2012 (30)	case-control	German	(a) PA	10	50.10 ± 11.00	4 (40.0%)	9
			EH	182	50.20 ± 15.70	74 (40.7%)	
			(b) PA before treatment	10	50.10 ± 11.00	4 (40.0%)	
			PA after treatment	10	51.20 ± 11.50	4 (40.0%)	
Maniero, 2012 (31)	case-control	Italy	(a) PA	44	50.00 ± 13.00	18 (40.9%)	9
			EH	61	50.00 ± 15.00	21 (34.4%)	
			(b) PA before treatment	31	-	-	
			PA after treatment	31	-	-	
Rossi, 1998 (32)	case-control	Italy	PA	16	50.80 ± 2.70	8 (50.0%)	7
			EH	16	48.50 ± 2.30	8 (50.0%)	
Rossi, 1995 (33)	case-control	Italy	(a) PA	10	52.40 ± 12.90	5 (50.0%)	6
			EH	20	46.00 ± 7.19	10 (50.0%)	
			HS	10	48.00 ± 12.70	5 (50.0%)	
			(b) PA before treatment	14	-	-	
			PA after treatment	14	-	-	
Lawrence, 1985 (34)	descriptive	American	PA	10	–	–	–

N, number; NOS, Newcastle-Ottawa Scale; PA, primary aldosteronism; NFA, non-functioning adrenal tumour; SA, secondary aldosteronism; GS, gitelman syndrome; BS, bartter syndrome; AI, adrenal incidentaloma; OP, osteoporosis; OE, osteopenia; HS, healthy subjects.

the serum calcium or urinary calcium level or the BMDs of the femoral neck and lumbar spine (Figure 4).

Publication bias

Publication bias in terms of PTH levels was sought in works that compared PA patients to EH subjects and PA patients before and after treatment. The funnel plots were substantially symmetrical, and the Egger's test revealed no obvious publication bias (Figure 5).

Sensitivity analysis

The median NOS score was 8. Thus, we repeated the analysis including only "high quality" studies (NOS ≥ 8). None of the AKP or BAP level, or the BMD, were included in sensitivity analysis because too few studies reported such data. After excluding "low quality" studies, the above data on urinary calcium and serum PTH levels were largely confirmed. In contrast, no significant differences were found between PA patients and EH subjects in terms of serum calcium levels, or between PA patients before and after treatment in terms of serum 25-OHD levels. However, the serum calcium level differed significantly between unilateral and bilateral PA patients (Table 2).

Subgroup analysis

All of study location (Asia or Europe), the assays used to measure serum PTH and 25-OHD, and the AVS procedure (with or without ACTH stimulation) might have affected our assessments; we thus performed three subgroup analyses. At least one such analysis eliminated the heterogeneity, except in terms of the serum calcium, PTH, and 25-OHD comparisons between PA patients and EH subjects (Table 3).

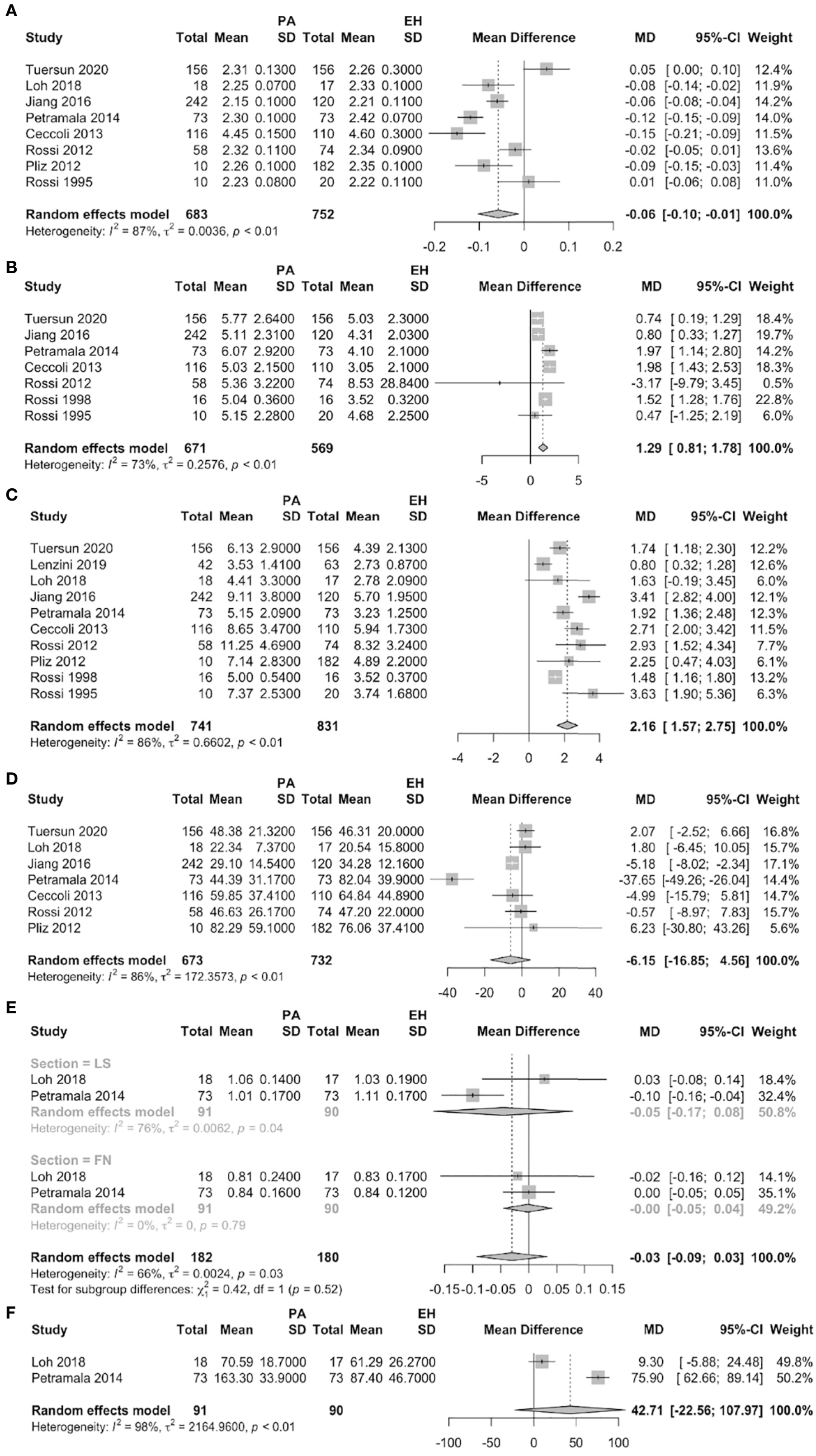

FIGURE 2
Forest plots of PA vs. EH patients (**A**: serum calcium, **B**: urine calcium, **C**: serum PTH, **D**: serum 25-OHD, **E**: BMD of FN and LS, **F**: AKP).

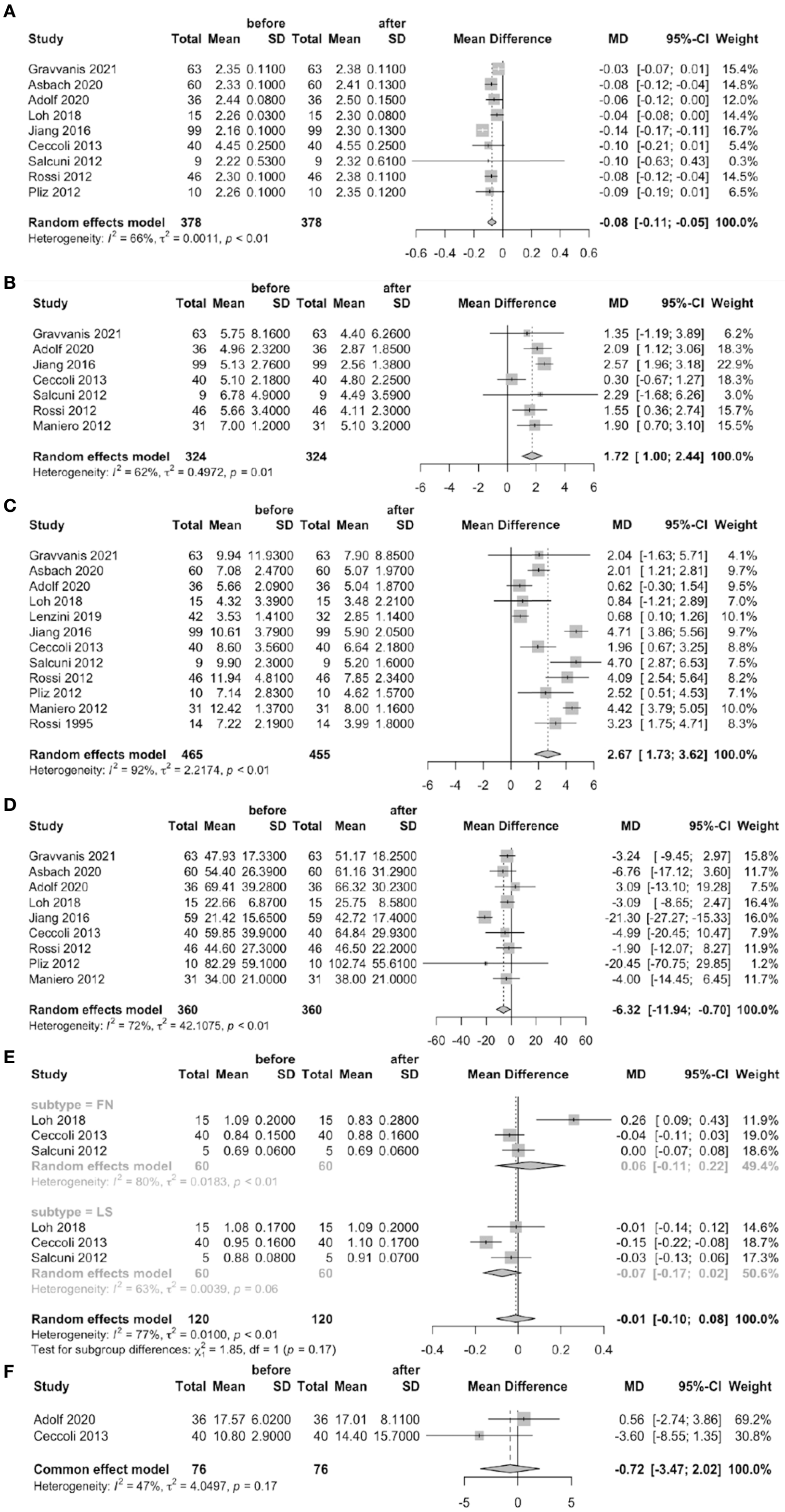

FIGURE 3
Forest plots of before-treatment vs. after-treatment PA patients (**A**: serum calcium, **B**: urine calcium, **C**: serum PTH, **D**: serum 25-OHD, **E**: BMD of FN and LS, **F**: BAP).

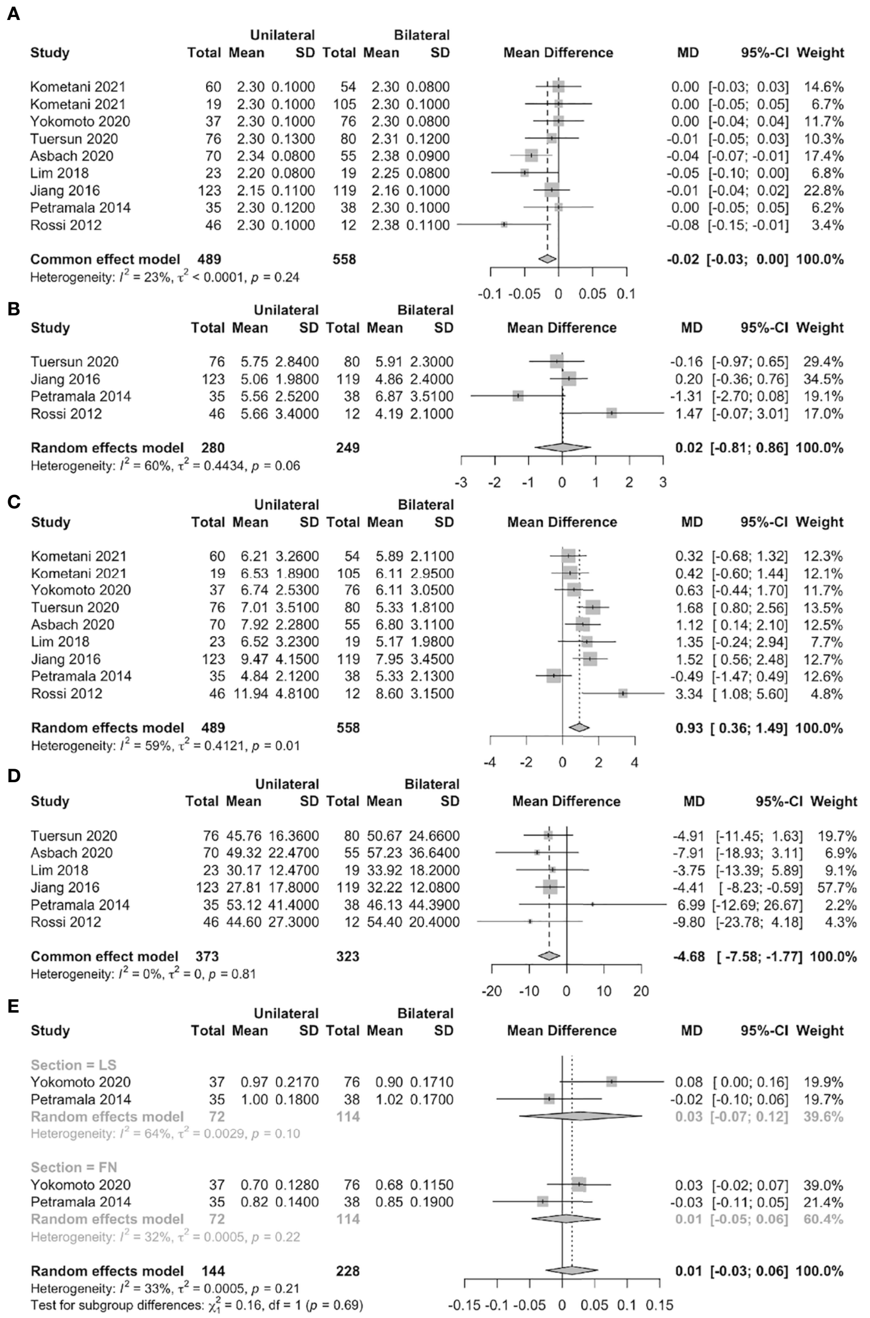

FIGURE 4
Forest plots of unilateral vs. bilateral PA patients (**A**: serum calcium, **B**: urine calcium, **C**: serum PTH, **D**: serum 25-OHD, **E**: BMD of FN and LS).

Discussion

We consistently found that PA patients (especially unilateral patients) were at higher risk of OP than EH subjects but the risk was reduced after medical treatment or surgery. Thus, aldosterone may affect both PTH secretion and bone metabolism.

Direct effects of aldosterone on bone metabolism

Excess aldosterone directly affects bone formation and resorption; inhibition of the RAAS system reduces bone loss (17). The following mechanisms may explain these phenomena. The long-term oxidative stress and chronic inflammation of PA patients

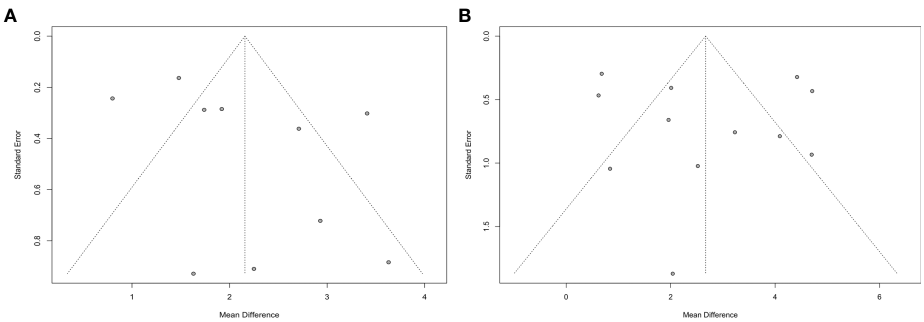

FIGURE 5
Funnel plots of meta-analysis on PTH (**A**: PA vs. EH, **B**: Before-treatment vs. After-treatment PA patients).

may increase osteoblast and osteocyte apoptosis (35), triggering abnormal bone metabolism, secondary OP, and even fracture (36), (37). It is well known that glucocorticoids can affect bone metabolism. Recently, mineralocorticoids have also been found to be related to bone metabolism. Researchers have found that MR antagonists (MRAs) reduced the risk of fracture in patients with secondary aldosteronism (38). Beavan et al. (39) reported (in 2001) that MR existed in human osteocytes; aldosterone may thus act directly on osteocytes. Later studies showed that several genes of the mineralocorticoid pathway (NR3C2, PIK3R1, PRKCH, and SCNN1B) may affect bone strength (40).

Aldosterone may affect bone metabolism by interacting with PTH or vitamin D

Resnick et al. (34) were the first to report elevated PTH levels in PA patients (in 1985). Many studies (14, 17, 18), (25–27, 29, 30), (32), (33) have confirmed this. A possible bidirectional interaction between aldosterone and PTH has been suggested (6), (7). Several studies have proposed that aldosteronism may cause secondary HPT by reducing sodium and calcium re-absorption by the proximal renal tubules (26), (27), (30), (32), increasing urinary calcium excretion, and long-term calcification. This explains why PA patients tend to have higher serum calcium but lower urinary calcium levels than others. It has been suggested that, in the acute phase, regulation of PTH secretion by the RAAS system is mediated by angiotensin II (Ang II), but aldosterone may be involved in such regulation in the chronic phase (41). PTH and calcium levels both affect aldosterone secretion; however, that is not our topic here.

PA patients more commonly exhibit vitamin D deficiency than others (42); vitamin D supplementation downregulates the RASS system (43), (44). We found no significant difference in serum 25-OHD levels between PA and EH patients, but the level increased significantly in PA patients after medical treatment or surgery,

TABLE 2 Sensitivity analysis on “high quality” studies (NOS≥8).

Item	N of studies	N of patients/controls	MD (95% CI)	I^2	P-value
PA vs. EH					
Serum calcium	4	466/532	-0.03 (-0.09, 0.03)*	84%	<0.01
Urine calcium	3	456/350	0.76 (0.41, 1.12)	0%	0.50
Serum PTH	4	466/532	2.59(1.69, 3.50)	82%	<0.01
Serum 25-OHD	4	466/532	-1.51 (-6.43, 3.41)	60%	0.06
Before-treatment vs. After-treatment PA					
Serum calcium	7	323/323	-0.08 (-0.11, -0.05)	70%	<0.01
Urine calcium	6	284/284	2.17 (1.70, 2.65)	0%	0.66
Serum PTH	8	354/354	3.19 (2.03, 4.36)	90%	<0.01
Serum 25-OHD	7	305/305	-7.00 (-14.13, 0.13)*	76%	<0.01
Unilateral vs. Bilateral PA					
Serum calcium	5	338/285	-0.03 (-0.04, -0.01)*	35%	0.19
Urine calcium	3	245/211	0.20 (-0.24, 0.64)	40%	0.19
Serum PTH	5	338/285	1.54 (1.04, 2.04)	0%	0.51
Serum 25-OHD	5	338/285	-4.94 (-7.87, -2.00)	0%	0.93

N, number; MD, mean difference; 95% CI, 95% Confidence Intervals; * MD results changed after excluding “low quality” studies.

TABLE 3 Subgroup analyses of study location, the assay used to measure serum PTH and 25-OHD, and the AVS procedure.

Item	Subgroup	N of studies	N of patients	MD (95% CI)	I^2	P-value for I^2	X^2
PA vs. EH							
Serum calcium	Asian	3	416/293	-0.03 (-0.11, 0.05)	88%	<0.01	0.81
	Europe	5	267/459	-0.07 (-0.13, -0.02)	87%	<0.01	
Urine calcium	Asian*	2	398/276	0.77 (0.42, 1.13)	0%	0.87	15.19
	Europe	5	273/293	1.59 (1.39, 1.80)	40%	0.15	
Serum PTH	1. Asian	3	416/293	2.37 (1.14, 3.59)	88%	<0.01	0.19
	Europe	7	325/538	2.05 (1.36, 2.75)	81%	<0.01	
	2. ECLIA	3	282/448	2.20 (1.46, 2.94)	55%	0.11	18.9
	ELISA	1	42/63	0.80 (0.32, 1.28)	-	-	
	CLIA	2	260/137	2.74 (1.04, 4.43)	70%	0.07	
	RIA	3	99/109	2.02 (1.12, 2.92)	71%	0.03	
	Mix	1	58/74	2.93 (1.52, 4.34)	-	-	
Serum 25-OHD	1. Asian	3	416/293	-0.16 (-6.34, 4.21)	76%	0.02	0.95
	Europe	4	257/439	-11.15 (-30.75, 8.45)	89%	<0.01	
	2. ECLIA	1	156/156	2.07 (-2.52, 6.66)	-	-	2.75
	ECLA	2	260/137	-2.81 (-9.29, 3.67)	59%	0.12	
	CLA	4	257/439	-11.15 (-30.75, 8.45)	89%	<0.01	
Before-treatment vs. After-treatment PA							
Serum calcium	Asian	2	378/378	-0.09 (-0.19, 0.01)	92%	<0.01	0.26
	Europe*	7	264/264	-0.06 (-0.09, -0.04)	0%	0.56	
Urine calcium	Asian	1	99/99	2.57 (1.96, 3.18)	-	-	5.16
	Europe*	6	225/225	1.46 (0.71, 2.20)	36%	0.17	
Serum PTH	1. Asian	2	114/114	2.89 (-0.89, 6.68)	91%	<0.01	0.01
	Europe	10	351/341	2.58 (1.60, 3.57)	91%	<0.01	
	2. ECLIA*	4	173/173	2.05 (1.42, 2.68)	0%	0.97	37.87
	CLA	1	36/36	0.62 (-0.30, 1.54)	-	-	
	CLIA	4	154/154	3.83 (2.22, 5.44)	75%	<0.01	
	ELISA	1	42/32	0.68 (0.10, 1.26)	-	-	
	Mix	1	46/46	4.09 (2.54, 5.64)	-	-	
	RIA	1	14/14	3.23 (1.75, 4.71)	-	-	
Serum 25-OHD	1. Asian	2	74/74	-12.16 (-30.01, 5.68)	95%	<0.01	0.86
	Europe*	7	286/286	-3.51 (-7.51, 0.49)	0%	0.95	
	2. ELISA	1	63/63	-3.24 (-9.45, 2.97)	-	-	26.77
	CLA*	5	192/192	-3.60 (-9.64, 2.44)	0%	0.81	
	ECLIA	1	15/15	-3.09 (-8.65, 2.47)	-	-	
	ECLA	1	59/59	-21.30 (-27.27, -15.33)	-	-	
	RIA	1	31/31	-4.00 (-14.45, 6.45)	-	-	
Unilateral vs. Bilateral PA							
Serum calcium #	1. Asian*	6	338/453	-0.01 (-0.01, 0.01)	0%	0.64	3.38
	Europe	3	151/105	-0.04 (-0.06, -0.01)	44%	0.17	
	2. With ACTH	4	149/255	-0.02 (-0.04, 0.00)	36%	0.19	1.11
	Without ACTH	5	340/303	-0.01 (-0.03, 0.01)	11%	0.34	
Urine calcium	Asian*	2	199/199	0.09 (-0.37, 0.54)	0%	0.47	0
	Europe	2	81/81	0.06 (-2.66, 2.78)	85%	<0.01	
Serum PTH	1. Asian*	6	338/453	0.99 (0.46, 1.51)	29%	0.22	0.02
	Europe	3	151/105	0.81 (-0.50, 2.12)	83%	<0.01	
	2. With ACTH*	4	149/255	1.12 (-0.90, 3.14)	0%	0.68	0.19
	Without ACTH	5	340/303	1.09 (-0.01, 2.19)	78%	<0.01	
	3. ECLIA*	5	262/370	0.87 (0.34, 1.40)	28%	0.23	5.94
	RIA	2	58/57	0.32 (-1.47, 2.11)	73%	0.05	
	CLIA	1	123/119	1.52 (0.56, 2.48)	-	-	
	Mix	1	46/12	3.34 (1.08, 5.60)	-	-	
Serum 25-OHD #	1. Asian*	3	222/218	-4.45 (-7.58, -1.33)	0%	0.98	0.14
	Europe*	3	151/105	-6.10 (-14.03, 1.82)	3%	0.35	
	2. With ACTH*	2	93/74	-5.55 (-12.81,1.70)	0%	0.58	0.07
	Without ACTH*	4	280/249	-4.51 (-7.68,-1.34)	0%	0.60	

(Continued)

TABLE 3 Continued

Item	Subgroup	N of studies	N of patients	MD (95% CI)	I^2	P-value for I^2	X^2
	3. ECLIA	1	76/80	-4.91 (-11.45, 1.63)	-	-	0.18
	CLA*	3	151/105	-6.10 (-14.03, 1.82)	3%	0.35	
	ECLA	1	123/119	-3.75 (-13.39, 5.89)	-	-	
	Unknown	1	23/19	04.41 (-8.23, -0.59)	-	-	

N, number; MD, mean difference; 95% CI, 95% Confidence Intervals; CLA, chemiluminescence assay; ECLA, electro-chemiluminescence assay; ECLIA, electro-chemiluminescence immunoassay; ELISA, enzyme linked immunosorbent assay; CLIA, chemiluminescent immunoassay; RIA, immunoradiometric assays; *I^2<50% in subgroup analysis; # I^2<50% before subgroup analysis.

suggesting that vitamin D might be involved in the action of aldosterone in terms of bone metabolism. Vitamin D increases the intestinal absorption of calcium and phosphorus, re-absorption of calcium and phosphate in the renal tubules, and bone calcium deposition. Reduced levels of serum vitamin D stimulate PTH secretion and upregulate the RAAS system (44–48); the 1,25(OH)$_2$D receptor complex inhibits the expression of renin *in vitro* (43), (49), (50). In PA patients, the level of the vitamin D receptor (VDR) may be associated with that of a marker of osteoclast activation, thus tartrate-resistant acid phosphatase 5b (TRACP-5b) (6). Fibroblast growth factor 23 (FGF23) is a phosphorylated protein regulated by phosphate and 1,25(OH)$_2$D. The latter stimulates the production of FGF23 and creates a negative feedback loop that regulates the production itself (51), as well as PTH secretion. FGF23 plays roles in PA-related HPT and improved parathyroid function after adrenalectomy in PA patients (52), but vitamin D supplementation does not completely correct HPT in PA patients (31), (10). Low vitamin D levels may (together with high aldosterone levels) affect PTH secretion and bone metabolism in PA patients, increasing the OP risk.

Risk of OP in PA patients

After excluding the effect of hypertension (23), PA patients still had a higher fracture risk than general populations (28), (13), (23), (22). Wu et al. (53) confirmed a high prevalence of such fractures in a prospective cohort study. The BMD is commonly used to evaluate bone strength. We found no significant difference in the BMD of either the lumbar spine or femoral neck before and after PA treatment. We did not meta-analyze the BMD data of works that compared PA and EH groups because there were few such studies. However, Petramala et al. (26) and Salcuni et al. (28) found that the osteopenia and OP rates in PA patients were significantly higher than in EH patients, healthy subjects, and those with adrenal non-functioning tumors (NFAs). This was confirmed by another study comparing patients with PA and secondary aldosteronism (9).

The trabecular bone score (TBS) is a new indicator of bone microstructure, used to evaluate bone quality and fracture risk. Several studies have suggested that aldosterone may trigger osteopenia by destroying bone microstructure rather than by reducing the BMD (5), (54); the TBS may be a better indicator than the BMD when screening for OP in PA patients. Although no significant BMD changes were evident in early-stage PA patients, bone turnover increased (as revealed by changes in the CTX and PINP levels) (18). Unfortunately, no study has used the TBS to compare EH and PA patients.

The effect of aldosterone on BMD remains controversial (28), (23), and the mechanism of that has not been fully elucidated. Furthermore, more research is needed on how aldosterone may affect bone metabolism and the possible association between TBS and aldosterone in the future.

Does bone metabolism differ between unilateral and bilateral PA patients?

This possibility remains controversial (14), (17), (25), (26), (29), (15), (11, 13, 19), (55), (56). All except three studies that we reviewed found that the serum PTH levels differed between unilateral and bilateral PA patients; the exceptions were Kometani et al., Jiang et al., and Riester et al. (25), (11), (55). Petramala et al. (26) found that patients with aldosterone-producing adenomas (APAs) exhibited more bone remodeling than did those with idiopathic hyperaldosteronism (IHA). Yokomoto et al. (13) reported that unilateral PA was an independent risk factor for vertebral fracture. We found that, in patients with unilateral PA, the serum PTH level was higher and the serum 25-OHD level lower than in patients with bilateral PA, which meant that a high serum aldosterone level is associated with a high serum PTH level, indicating that unilateral PA patients are at higher risk of sHPT.

Strengths and limitations

There were 2 meta-analyses before our research. Loh et al. (4) published a conference abstract in 2019, meta-analyzing the difference between PA (n=352) and non-PA (n=587) patients, and between before and after treatment in PA patients. Shi et al.

(3) just meta-analyzed the difference between PA and EH patients with 15 articles in 2020. Unlike previous work (3), (4), we are the first to review systematically and meta-analyze the possible effects of PA subtypes on bone metabolism. The number of included papers and the sample size of the present study are larger than those of the previous work. However, certain limitations of our work should be acknowledged. First, most included studies were observational and had small patient numbers. Second, the assays used to measure the levels of plasma aldosterone, and serum PTH and 25-OHD, varied. Third, some studies evidenced heterogeneity. Although the sensitivity analyses eliminated most heterogeneity, a possibility of bias remains. Fourth, few works dealt with the effects of different PA subtypes on BMD; we could engage in only descriptive analyses.

Conclusion

Excess aldosterone was associated with decreased serum calcium, elevated urinary calcium, and elevated PTH levels; these effects may be enhanced by low serum 25-OHD levels. The risks of OP and fracture might be elevated in PA patients, especially unilateral PA patients, but could be reduced after medical treatment or adrenal surgery. The lack of BMD changes after treatment, indicates, however, that PTH and calcium changes may also represent an epiphenomenon of limited clinical significance, so more research is needed, either to confirm, or to refute the notion of any significant change in fracture rate in PA patients. TBS may be a better indicator than BMD when screening for OP in PA patients. More research is needed on how aldosterone may affect bone metabolism and the possible association between TBS and aldosterone.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

AW and ZL designed the study. HL and XH collected the data. AW performed the meta-analysis and drafted the manuscript. JL, HX, ZN and LZ partially planned the research. ZL edited the manuscript. All authors contributed to the article and have approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2022.1027841/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Subgroup analysis of PA and EH (**A**: serum calcium, **B**: urine calcium, **C**: serum PTH, **D**: serum 25-OHD).

SUPPLEMENTARY FIGURE 2
Subgroup analysis of before-treatment and after-treatment PA patients (**A**: serum calcium, **B**: urine calcium, **C**: serum PTH, **D**: serum 25-OHD).

SUPPLEMENTARY FIGURE 3
Subgroup analysis of unilateral and bilateral PA patients (**A**: serum calcium, **B**: urine calcium, **C**: serum PTH, **D**: serum 25-OHD).

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