Journal of Clinical & Translational Endocrinology 41 (2025) 100401

Contents lists available at ScienceDirect

Journal of Clinical & Translational Endocrinology

journal homepage: www.elsevier.com/locate/jcte

Glucocorticoids: The culprit behind metabolic disorders in primary Aldosteronism? A narrative review

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ARTICLE INFO

Keywords:
Primary aldosteronism
Metabolic syndrome
Obesity
Dyslipidemia
Diabetes
Cortisol

ABSTRACT

In recent years, a new approach toward aldosterone secretion autonomy has emerged as a consequence of studies demonstrating its continuum from subclinical, mild to overt and severe forms. These clinical insights were accompanied by immense progress in deciphering the tissue and cellular pathology underlying primary aldosteronism (PA).

Thus far, research has not sufficiently elucidated the relationships between overt PA and metabolic disorders. Similarly, the role of glucocorticoid cosecretion in this patient group remains unclear. Milder than overt PA forms have been scarcely investigated.

This review critically analyzes these issues on the basis of a literature search of the PubMed database.

Introduction

Recent studies have shown a continuous spectrum of renin-independent aldosteronism, much of which is not identified by current diagnostic criteria for primary aldosteronism (PA). All forms of autonomous aldosteronism – both those meeting conventional criteria and the less severe ones – contribute to or cause hypertension (HT) in up to 30 % of unselected patients [1,2]. All presentations of aldosterone (Ald) autonomy encompass normokalaemia and normotension (NT), isolated hypokalaemia, grade 1 through 3 HT (with either normo- or hypokalaemia), and several biochemical constellations, including positive screening with negative confirmatory test results as well as the opposite [3–7].

Clinical data on the continuity of PA have been supported by discoveries in the cellular and tissue pathology associated with Ald excess. The introduction of Ald synthase (CYP11B2) immunohistochemistry and next-generation sequencing (pinpointing Ald-driving mutations) revolutionized our understanding of Ald-producing lesions. Consequently, a recent histopathological consensus categorizes them as Ald-producing: adrenocortical carcinoma, diffuse hyperplasia (APDH), adenoma (APA), nodule (APN), and micronodule (APMN), multiple Ald-producing nodules (MAPN) and multiple Ald-producing micronodules (MAPMN) [8]. The concomitance of different lesions in one patient is frequent [9,10]. While in the past, 'bilateral adrenal hyperplasia' and 'idiopathic hyperaldosteronism' were used to describe the main PA subtype in opposition to an APA, these terms are referred to here as 'non-lateralized' or 'bilateral' PA. In fact, histpathological studies showed that the lack of clear asymmetry in Ald secretion between both adrenals is very rarely underlain by APDH and much more commonly results from the presence of bilateral APMNs, APAs or multiple APNs [10,11]. The variety of PA-causing lesions should be considered when interpreting research on metabolic disorders, *e.g.,* to what extent is it justified to compare data from patients with lateralized APAs and bilateral cases with possibly similar pathology.

Evidence of a continuous PA spectrum warrants approaching metabolic disorders in its course anew, since previous studies investigated almost always only overt PA presentations. For the total diabetic and hypertensive populations, the following relationships are widely known: diabetes mellitus (DM) is present in approximately 20–30 % of all hypertensive patients [12], whereas approximately half to two-thirds of all diabetic patients have comorbid HT [13]. Consequently, bearing these proportions in mind, deleterious effects of renin-independent aldosteronism on the metabolic homeostasis may be underestimated. Systematic testing using a conventional approach confirms PA in 11 to 22.2 % of hypertensive patients with DM/hyperglycemia [14–17]. However, in a study that applied PA diagnostic thresholds based on healthy (normotensive) individuals, an Ald suppression test that combined intake of dexamethasone (DXM), captopril, and valsartan demonstrated

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https://doi.org/10.1016/j.jcte.2025.100401
Received 25 February 2025; Received in revised form 14 May 2025; Accepted 26 May 2025
Available online 28 May 2025

a 34.2 % PA prevalence among patients with HT and concomitant DM [18].

This narrative review discusses research on metabolic disorders across the spectrum of renin-independent aldosteronism by first considering subclinical/mild presentations, followed by studies on overt PA patients. Non-overt PA is referred to here as subclinical PA or autonomous Ald secretion (AAS), as proposed previously [4]. In brief, AAS cases only meet one of the two conventional PA diagnostic criteria: either a positive screening test, *i.e.*, elevated Ald-to-renin ratio (ARR), or a positive confirmatory PA test (the saline infusion test, SIT, the oral salt loading test, OSLT, the captopril challenge test, CCT, or the fludrocortisone suppression test, FST) [19]. Concerning metabolic disorders in the course of overt PA, the review focuses on their prevalence, characteristics across the main PA subtypes, the effects of PA-targeted therapy but particularly highlights the role of cortisol cosecretion.

Methods

The review is based on a literature search of the PubMed database performed on February 8, 2025. Publications concerning humans, written in English, and with an available abstract were qualified for screening. A combination of terms from two of the following groups were the basis of the search: (1) 'primary aldosteronism', 'primary hyperaldosteronism', 'aldosteronism' or 'aldosterone' in the title, and, (2) 'diabetes', 'prediabetes', 'pre-diabetes', 'dyslipidemia', 'hypercholesterolemia', 'cholesterol', 'triglyceride', 'carbohydrate' or 'lipid' in the title or abstract. The search yielded 597 results. Titles, abstracts, and, in part, full texts were screened for inclusion in this review. Based on references from included publications, 14 further articles were added.

In the case of AAS/subclinical PA, only original articles were considered. However, in the case of overt PA, rather than analyzing all past studies in detail, recent *meta*-analyses and original articles not included in them were used to consider available research. With respect to the latter, focus was placed on sex-, age-, and BMI-matched studies for comparisons between PA patients and primary HT patients.

Metabolism disorders in subclinical PA/Autonomous aldosterone secretion

In contrast to PA, which requires meeting the diagnostic criteria, AAS is not a widely recognized disorder, therefore; research on metabolic disorders in its course is sparse. The continuous nature of Ald autonomy makes it impossible to draw a clear line between overt PA and AAS as well as AAS and physiology. As mentioned above, AAS/mild PA can be present both in NT and HT [4,7].

In a study by Luo et al., patients with low-renin HT (*i.e.*, with plasma renin activity, PRA, below 1 ng/ml/h) were investigated for PA [20]. To test positive in PA screening required a minimal Ald of 9 ng/dl and an ARR of 20 (ng/dl per ng/ml/h). A positive SIT required an Ald of 10 ng/dl or higher for overt PA, and the 5–10 ng/dl range was categorized as mild PA. The results revealed that in 118 patients with positive ARR but negative SIT (defined here as AAS), the prevalence of diabetes mellitus (DM) was 11 %, which was significantly lower than that among 160 patients with overt PA (20 %) and comparable to that of 268 patients with mild PA (11.2 %). While screening criteria may have misclassified some patients, these data from a specialized HT center indicate a higher DM incidence in overt PA than in mild PA or AAS.

An association between metabolic syndrome (MetS) and AAS can be derived from the data of 356 patients of African descent analyzed in a family-based study [21]. The fact that PRA was suppressed in a majority of participants indicates Ald autonomy: in those with MetS, median PRA was 0.44 ng/ml/h (interquartile range, IQR, 0.41), whereas it was even lower in those without MetS. Multivariable models revealed that Ald was positively associated with MetS in all subjects and waist circumference in men, and negatively associated with high-density lipoprotein cholesterol (HDL-C). On the other hand, PRA was positively associated with triglyceride (TG) and fasting glucose levels, which points to a non-PA mechanism.

Similarly, Hundemer et al. reported that among 663 subjects extracted from a Hypertensive Pathotype cohort, a lower ability to stimulate PRA (by upright posture and a low-salt diet) was associated with higher BMI, age, HT and female sex [22]. Patients in the lowest tertile for renin stimulation ability had higher ARR and 24-h urinary Ald excretion (UAldE) than did those in the remaining two tertiles (intermediate and physiological, *i.e.*, high, ability to stimulate renin).

Furthermore, associations between Ald (but not PRA) and the presence of MetS, its components and indices of insulin resistance (IR) were recorded in a multicenter study of 829 individuals [23]. The lack of clear dependence of Ald on renin points to a biochemical PA/AAS constellation, along with a trend toward a higher ARR in those with MetS than in those without MetS. However, the mean ± standard deviation PRA was 2.5 ± 3.7 ng/ml/h; therefore, the majority of the subjects did not exhibit clear Ald autonomy.

In a population-based cohort of postmenopausal women and men older than 50 years, 89 patients with low-renin (PRA < 1 ng/ml/h) HT (LRH) could be characterized as AAS cases to a significant extent, since the median (IQR) Ald was 15.6 ng/dl (12.8–19.1) [24]. A comparison with non-LRH subjects (n = 167, including normotensive and hypertensive patients) revealed greater dyslipidemia but a lower DM incidence in the LRH group. A possible overlap between groups (*e.g.,* PRA between 0.75 and 1 on a continuum with >1 ng/ml/h), the lack of matching, inclusion of normotensives in the non-LRH group, and the lack of information on lipid-lowering therapy are factors rendering conclusions on metabolic disorders difficult. However, adjusted analyses showed an association between LRH (indicative of AAS) and osteoporosis.

In a smaller study, 40 nondiabetic PA patients were matched for age, sex, BMI, BP and HT duration with patients with LRH [25]. For the former, strict screening criteria were applied, *i.e.,* combined minimal Ald-to-PRA ratio ARR of 40 and minimal Ald of 15 ng/dl. For this reason, among the LRH patients, the majority presented biochemical AAS/mild PA features, with a mean ARR of 48 ± 34 and Ald of 24.1 ± 10.6 ng/dl. With respect to metabolic disorders, the homeostasis model assessment (HOMA) for IR index (HOMA-IR) and adiponectin were comparable between patients with MetS in both groups (PA and low-renin HT). Conversely, in subgroups without MetS, overt PA patients were characterized by higher HOMA-IR and lower adiponectin. These findings highlight a less significant role of Ald than that of obesity-related mechanisms in metabolic disorders among patients with AAS/mild PA, which contrasts with overt PA patients.

On the one hand, obesity is associated with stimulation of the renin-angiotensin-aldosterone system (RAAS), resulting in renin-dependent aldosteronism [26]. On the other hand, adipogenic factors have been shown to stimulate Ald independently of renin, which renders differentiating between the primary and secondary natures of Ald excess difficult in the setting of low or equivocal renin [27]. For example, in a study of nearly 400 Afro-American adults below the age of 55, the mean supine PRA was significantly higher at 1.1 ± 0.1 ng/ml/h in normotensive participants (approximately 55 % of total) than in patients with HT at 0.7 ± 0.07 ng/dl, whereas Ald was 33 % higher in the latter [28]. Moreover, Ald correlated positively with waist circumference, total cholesterol (TC), triglyceride (TG), HOMA-IR, and BP, whereas PRA correlated negatively with BP. Participants with MetS (17 %) had higher Ald and ARR than those without MetS.

To summarize, dissecting the effect of subclinical PA/AAS (primary, renin-independent Ald excess not meeting overt PA criteria) on metabolic disorders is challenging because of possible concomitant Ald secretion secondary to insulin and/or adipocytokines, *i.e.*, stimulation of the RAAS in the course of obesity. There are insufficient data to clearly associate mild Ald excess with metabolic disorders (see Table 1).

Table 1
Selected studies on metabolic disorders in patients with possible autonomous aldosterone secretion.

Author, year	Study participants	AAS indicated by:	Findings concerning Ald autonomy and metabolic disorders
Luo,2019	546 pts with low-renin HT	ARR > 20 ng/dl per ng/ml/h	DM prevalence 20 % in overt PA (Ald > 10 ng/dl in SIT) versus ca. 11 % in mild PA (5–10 ng/dl)/AAS
Bochud, 2006	356 pts of African descent	median (IQR) PRA 0.44 (0.41)	Ald associated "+" with MetS, waist circ. in men, "–" with HDL-C, but PRA "+" with FBG and TG
Hundemer, 2017	663 pts from the Hypertensive Pathotype cohort	ability to stimulate renin (low-salt diet, upright posture)	lowest tertile had higher ARR, UAldE; low ability associated with higher BMI, age, HT, female sex
Lee, 2024	population-based cohort: postmenopausal women, men aged > 50,	89 patients with PRA < 1 and median Ald of 15.6 (12.8–19.1);	pts with low-renin characterized by greater dyslipidemia yet lower DM prevalence than 167 pts with PRA ≥ 1 (lipid-lowering drugs not reported)
Fallo, 2007	40 PA pts matched with 40 pts with "low-renin" HT	ARR = 48 ± 34, Ald = 24.1 ± 10.6 in low-renin pts, PA diagnosis required Ald > 15	HOMA-IR and adiponectin comparable in pts with Mets in both groups; in overt PA pts without MetS HOMA-IR and adiponectin higher
Kidambi, 2007	400 Afro-Americans below the age of 55; HT in ca. 45 %	pts. with HT had a PRA of 0.7 ± 0.1 and 33 % higher Ald than pts with NT	Ald correlated "+" with waist circ., TC, TG, HOMA-IR, BP; PRA "–" with BP; Ald and ARR 17 % higher in those with MetS than without

Legend: Aldosterone concentration in ng/dl; PRA is given ng/ml/h; "+" – positively; "–" – negatively; AAS – autonomous aldosterone secretion; Ald – aldosterone; ARR – aldosterone-to-renin ratio; BMI – body mass indes; BP – blood pressure; circ. – circumference; DM – diabetes mellitus; FBG – fasting blood glucose; HDL-C – high density lipoprotein cholesterol; HOMA-IR – homoeostasis model assessment of insulin resistance index; HT – hypertension; IQR – interquartile range; MetS – metabolic syndrome; NT – normotension; PA – primary aldosteronism; pts – patients; PRA – plasma renin activity; SIT – saline infusion test; TC – total cholesterol; TG –triglycerides; UAldE – 24-hour urinary aldosterone excretion.

Metabolic disorders in overt PA

Multiple factors render investigating metabolic disorders in PA difficult, including overweight/obesity, age, medications, physical activity, and possible cortisol cosecretion. Moreover, PA diagnostic criteria vary (especially with respect to screening) and do not account for the continuum of abnormal Ald secretion [29].

Carbohydrate metabolism disorders. Significance of cortisol cosecretion

Both *meta*-analyses and individual studies demonstrated a greater prevalence of abnormal glucose metabolism in PA patients than in the general population (*e.g.*, [30,31]) but this was true only for some reports comparing PA with primary HT patients [32–41]. Nevertheless, in a recent (2022) *meta*-analysis of 26 studies involving approximately 53 000 patients, albeit with moderate heterogeneity, a higher prevalence of DM (relative risk, RR, 1.54, 95 % confidence interval, CI: 1.2; 1.98) and impaired glucose tolerance, IGT, (RR 1.99, 95 % CI: 1.74; 4.16) was demonstrated in PA patients than in those with primary HT, whereas the prevalence of impaired fasting glucose (IFG) was comparable [42]. In studies with matching (for sex, age, and BMI) the RR for DM was 1.33 (95 % CI: 1.04; 1.69). With respect to other parameters, PA patients had a lower HOMA of the beta-cell function index than primary HT patients (five studies analyzed), while other parameters were comparable (among them, fasting glucose, HbA1c, 2-h OGTT, and HOMA-IR). Diminished beta-cell function was speculated to result from islet cell damage and shown not to result from hypokalaemia [43,44].

A 2018 *meta*-analysis reported similar results upon investigating nine studies with 2007 PA and 5341 primary HT patients: the OR for DM in the former was 1.33 (95 % CI: 1.01; 1.74) overall, 1.39 (95 % CI: 1.17; 1.66) for five studies with matching, and 2.02 (95 % CI: 1.25; 3.25) for four prospective studies [45].

The above results point to a clear association between excess Ald and carbohydrate metabolism disorders. However, the effect of Ald can be questioned *in lieu* of that of cortisol. In a large (2210 PA patients) 2019 Japanese study, although DM was more prevalent in PA patients than in the general population, the difference was driven mainly by suspected subclinical hypercortisolemia (currently mild autonomous cortisol secretion, MACS) on the basis of the overnight 1-mg DXM suppression test (DST) [32]. DM prevalence among PA patients with a negative DST (cortisol < 50 nmol/l) was comparable to that of age-, sex- and BMI-matched primary HT patients (21.1 % *vs* 14.2 %, p = 0.06). Conversely, the DM prevalence was lower in patients without MACS (16.9 %) than in those with MACS: 16.9 % versus 26.8 %, p < 0.001. Furthermore, suspected MACS was associated with DM and prediabetes, with an adjusted OR of 1.81 (95 % CI: 1.14; 2.87). This was not the case for Ald or potassium levels. In fact, despite more severe PA in lateralized disease, prediabetes was more prevalent in the non-lateralized subtype [32].

The significance of cortisol excess even below the MACS threshold for the prevalence of DM was reported in a multicenter retrospective study of the same population [46]. Bilateral PA patients with (n = 196) adrenal tumors on computed tomography had higher DST cortisol than patients with normal adrenal morphology (n = 331): 30.5 *vs* 24.9 nmol/l, as well as higher DM prevalence: 19 *vs* 10.6 % (p < 0.01). However, at the same time, PA was more severe in patients with adrenal tumors (evidenced by more frequent potassium supplementation, longer HT duration and higher ARR).

Furthermore, in a retrospective study of a Chinese population, 22 APA patients with cortisol cosecretion were compared with those with pure APAs at a 1:4 ratio [47]. These groups were comparable in terms of PA severity, age, BMI, and sex, however, glucose intolerance or DM was significantly more prevalent in the former: 59.1 % versus 21.7 %.

A report of 161 prospective patients from the German Conn Registry supports the relevance of MACS in carbohydrate dysmetabolism. At least one abnormal hormonal test indicative of excess cortisol (elevated 1 mg DST cortisol, late night salivary cortisol and/or 24-h urinary cortisol excretion) was reported in 77.6 % of patients [48]. DM was diagnosed in 20 % of those with a positive overnight DST result versus 0.8 % of those with a negative result.

In another European study, involving 174 consecutive PA cases from five centers, highly relevant data were reported. Total glucocorticoid but not mineralocorticoid metabolite excretion correlated positively with HOMA-IR and waist circumference, and negatively with HDL-C among PA patients [49]. Only "very few patients" out of 46 with a unilateral APA exhibited DST cortisol results characteristic of MACS, which contrasted with significantly increased total glucocorticoid output in 24-h urinary steroid metabolome analysis. Glucocorticoid excess in these unilateral PA patients was comparable to that of patients with MACS. Importantly, adrenalectomy normalized Ald and glucocorticoid excess. The significance of glucocorticoid excess was confirmed by an impaired

response in the cosyntropin test (30-minute cortisol < 430 nmol/l) after adrenalectomy in 13 of 45 prospective patients with an APA [49].

In a study based on the German PA registry, a positive correlation between post-DST cortisol and TC was found in a multivariable regression analysis among 1:1 age- and sex-matched PA patients with and without MACS (n = 47 per group), with a multiple $R^2 = 0.85$, p = 0.03 [50]. No correlations were recorded for cortisolaemia above 49.7 nmol/l, fat tissue amount, or muscle volume.

Contrasting data concerning the significance of excess glucocorticoid secretion in the course of PA in metabolic disorders were reported by Kwak et al. in a case-control study with 267 PA patients and 816 age-, sex-, and BMI-matched controls, who were mainly (62 %) normotensive [51]. Hyperglycemia (*i.e.,* DM and prediabetes) was more prevalent in PA patients than in controls: 55.6 % versus 37.6 % (p < 0.001), regardless of the presence of autonomous cortisol secretion, which was present in ca. 15 % of patients on the basis of a stricter definition (overnight DST cortisol above 138 nmol/l or above 61 nmol/l combined with an additional hormonal criterion). However, what probably affected the differences between controls with both PA subgroups was lower daily regular physical activity in the cases than in the controls: 17.8 % versus 44 %, p < 0.001.

No difference in DM prevalence was found for PA patients with (n = 24) and without MACS (n = 68) in a retrospective study from a tertiary Turkish cohort of adrenal adenoma patients examined between 2015 through 2024: 20.8 versus 16.2 %, p = 0.61 [52]. A small sample size clearly limits definitive conclusions.

Also countering the importance of cortisol cosecretion with respect to prediabetes and DM in PA, in a Chinese PA cohort (n = 729 total), differences in carbohydrate parameters between patients with negative (n = 344) and positive (n = 38) 1-mg DST were not significant [53]. Therefore, post-DXM cortisol was not considered in subsequent analyses concerning abnormal glucose metabolism, whereas Ald was independently associated with it, since, among others, in an adjusted model, the higher the Ald level, the more prevalent the DM was: OR was 1.89 (95 % CI: 1.26; 2.8) and 2.31 (95 % CI: 1.55; 3.43), respectively, in the second and third versus first Ald tertile. In MACS patients, a trend (not statistically significant) toward higher Ald was recorded.

However, in a prospective Taiwanese TAIPAI cohort (n = 436), propensity score matching revealed a higher DM prevalence in PA patients with MACS (n = 93) than in those without MACS: 25.8 % versus 11.5 % [54]. Additionally, Ald and ARR were higher in the former. The TAIPAI and the last-mentioned Chinese cohort studies highlight how approaches to analyzes probably account for disparate conclusions, *i.e.*, baseline versus post-DXM cortisol investigated; adjustment versus propensity score matching; additionally, affecting the ability to detect differences, there were twice as many MACS patients in the Taiwanese (21.3 %) as in the Chinese cohort (9.9 %) [53,54].

Two other TAIPAI cohort studies further indicate the effect of cortisol and not Ald on DM in PA. A post-DXM cortisol of at least 73 nmol/l was associated with new-onset DM independently of Ald, with a hazard ratio of 3.5 according to the Cox proportional hazards model [55]. In MRA-treated APA patients, elevated post-DST cortisol translated to an hazard ratio (HR) of 5.72 for new-onset DM, whereas post-adrenalectomy, the risk was comparable between patients with low and high post-DXM cortisol. In a more recent prospective study from the same registry, DM prevalence was 25.4 % in APA patients with MACS (50 nmol/l DST cortisol cutoff, n = 101 total) versus 14.4 % without MACS (n = 382), p = 0.01 [56].

In a 2024 study from the Chinese population, the DM prevalence in lateralized PA patients with a positive 1-mg DXM DST (n = 65) was more than twice that in those with a negative DST (n = 515): 18.5 % versus 9.1 %, p = 0.02, despite comparable PA severity although higher age (52.8 ± 8.7 versus 46.7 ± 11.2 years, respectively) [57]. The median adrenal tumor size was also 17.6 % higher in DST-positive PA patients, which points at the importance of the corticoid-producing tissue volume.

Taken together, the above data point to glucocorticoids as a culprit for carbohydrate metabolism disorders in PA patients (Table 2). Ald and cortisol cosecretion (sometimes referred to as 'Connshing' syndrome) requires further studies to discern the effects mediated by each hormone. At the moment, based on seven studies discussed above (one TAIPAI cohort study with both PA subtypes was selected instead of APAs only), the pooled RR for DM prevalence/incidence in PA patients with versus those without MACS (diagnosed as per the 50 nmol/l 1 mg overnight DST threshold) is 2.1 (95 % CI: 1.02; 4.31) in the random

Table 2
Impact of cortisol cosecretion on DM prevalence/incidence in primary aldosteronism.

First author, year	Study type, population	DST (+)/(−) pts	Findings concerning DM prevalence/incidence
Akehi, 2019 [32]	retrospective, multi-center Japanese cohort	209/681	DM prevalence 26.8 % in DST (+) *vs* 16.9 % in DST(−) pts, RR: 1.59 (95 % CI: 1.2; 2.1)
Gerards, 2019 [48]	prospective, two-center German cohort	34/127	OGTT revealed: DM in 20 % (7/34) of DST(+) pts, 0.8 % (1/126) of DST(−) pts; comparable prediabetes prevalence
Arlt, 2017 [49]	prospective, multi-center, European cohort	ND	urinary steroid metabolome profiling revealed glucocorticoid excess in 220 PA pts was comparable to that of 104 MACS (non-PA) pts and correlated with metabolic disorders (mineralocorticoid output did not)
Kunchel, 2024 [58]	retrospective, multi-center, European cohort	ND	a.o. 99 PA and 58 primary HT pts; in PA pts cortisone, cortisol and DHEA but not Ald was associated with metabolomic differences
Zhang, 2022 [53]	retrospective, single center, Chinese cohort	38/344	DM prevalence 18.4 % in DST (+) *vs* 15.4 % in DST(−) pts, RR 1.2 (95 % CI: 0.59; 2.44) – n.s.
Tsai, 2022* [54]	prospective, multi-center, Taiwanese cohort	101/333	Crude RR for DM prevalence in DST(+) *vs* (−) PA pts: 2.04 (95 % CI: 1.32; 3.15);RR after 1:3 PSM: 2.24 (95 % CI: 1.36; 3.67)
Tsai, 2025* [56]	prospective, multi-center, Taiwanese cohort	101/382	DM prevalence 25.4 % in DST (+) *vs* 14.4 % in DST (−) PA pts, RR: 1.72 (95 % CI: 1.13; 2.61)
Wu, 2023 [55]	prospective, single center, Taiwanese cohort	87/268	crude HR for DM incidence in PA pts with DST cortisol ≥ 73 nmol/l (n = 330) *vs* < 73 nmol/l (n = 57): 2.2 (95 % CI: 0.99; 4.93); adj., time-varying (adrenalectomy as a competing risk) HR: 2.33 (1.02; 5.5); estimated# RR for DM incidence in DST(+) *vs* (−) PA pts: 1.36 (95 % CI: 0.67; 2.77) – n.s.
Jiang, 2024 [57]	retrospective, single center, Chinese cohort	65/515	DM prevalence 18.5 % in DST (+) *vs* 9.1 % in DST(−) lateralized PA pts, RR: 2.02 (95 % CI: 1.13; 3.61)
Barlas, 2025 [52]	retrospective, single center, Turkish cohort	24/58	DM prevalence 20.8 % in DST (+) *vs* 16.2 in DST(−) pts, RR: 1.29 (95 % CI: 0.5; 3.33) – n.s.

Legend: Data from publications were extracted to provide counts of patients and calculate the relative risk of diabetes; * – in the 2025 study by Tsai et al. probably includes most of the 2022 study cohort; # - counts of patients with DST cortisol <50 and ≥50 nmol/l were estimated based on data provided in the study; a.o. – among others; Adj. – adjusted; Ald – aldosterone; DST – overnight 1-mg dexamethasone suppression test, which was considered positive for cortisol >50 nmol/l; HR – hazard ratio; MACS – mild autonomous cortisol secretion, *i.e.* with positive DST but without overt Cushing's syndrome signs; ND – no data; n.s. – not significant; PSM – propensity score matching; pts – patients; RR – relative risk.

effects model. Methodological differences between studies (*i.e.*, design, different subtype proportions, ethnicities, *etc.*) are indicated by high heterogeneity.

Dyslipidemia, metabolic syndrome and non-alcoholic fatty liver disease

In light of these associations, cortisol excess should also be considered in comparing the prevalence of MetS in PA versus primary HT patients (Table 3). However, adrenal hormone cosecretion was not accounted for in a 2024 *meta*-analysis of 12 studies (prevalence of MetS comparable between PA and primary HT patients in general, higher for overweight and obese subjects) [59], nor in the above-mentioned *meta*-analysis (eight studies for this outcome), which revealed an OR of 1.52 (95 % CI 1.22–1.91) for MetS in PA versus primary HT patients [45]. Inclusion criteria most likely account for the contrasting findings of the two *meta*-analyses. With HT present in both patient groups and comparable abdominal obesity due to matching (for age, sex, and BMI), the diagnosis of MetS depended only on the presence of DM/prediabetes and/or dyslipidemia. As discussed above, the former is more prevalent in PA patients, however, data on lipid profiles tell a different story.

In a 2022 *meta*-analysis of 30 studies, patients with primary HT presented more lipid abnormalities than did those with PA [60]. While HDL-C levels were comparable (with a trend toward higher HDL-C in PA), the standardized mean differences for TC, TG and low-density lipoprotein cholesterol (LDL-C) favored PA patients versus primary HT patients at −0.30 mmol/L (95 % CI: −0.41; −0.19), −0.17 mmol/L (95 % CI: −0.27; −0.08), and −0.16 mmol/L (95 % CI: −0.25; −0.07), respectively. The authors of the analysis suggested several underlying mechanisms, including glomerular hyperfiltration in PA, and hyperlipidemia associated with the use of thiazides in primary HT. The same result concerning TG was found in a 2024 *meta*-analysis of 12 studies [59].

Two original studies analyzed nonalcoholic fatty liver disease (NAFLD) in PA. Its prevalence was comparable in a European study of PA and low-renin HT patients (n = 40 for both groups) but higher in a larger cohort (n = 222 for both groups) from an Asian population: 35.1 % versus 29.7 %, with hypokalaemic PA patients exhibiting a higher prevalence of both NAFLD and DM [61,62]. The reason for this discrepancy may be that the low-renin group can be categorized as AAS/mild PA, with mean Ald of 20.5 ± 7.6 ng/dl, and ARR of 45 ± 37 ng/dl per ng/ml/h (unequivocally positive). In neither of these studies was cortisol cosecretion accounted for, which limits possible inferences of an association between PA and NAFLD.

Table 3
Dyslipidemia, metabolic syndrome and non-alcoholic fatty liver disease in PA compared to primary hypertension patients.

First author, year	Study type, population	No of PA and primary HT pts	Findings concerning metabolic disorders other than prediabetes and DM
Sun, 2024 [59]	*meta*-analysis, 12 studies	209 PA, 681 primary HT pts	MetS prevalence comparable in all pts, higher in PA pts in the obese and overweight subgroup (OR 1.45, 95 % CI: 1.17, 1.81); TG lower in PA pts
Monticone, 2018 [45]	*meta*-analysis, MetS analyzed in 8 studies	3162 total	OR for MetS 1.52 (95 % CI 1.22–1.91) in PA *vs* primary HT pts
Manosroi, 2022 [60]	*meta*-analysis, 30 studies	11,175 total	primary HT pts had comparable HDL-C, but higher TC, LDL-C and TG compared to PA pts (possibly due to glomelular hyperfiltration? thiazides in primary HT?)
Fallo, 2010 [61]	prospective, four specialized HT clinics, Italian	40 PA and 40 low-renin HT pts	comparable nonalcoholic fatty liver disease prevalence, probable mild PA in the low-renin HT group
Chen, 2021 [62]	cross-sectional, single center, Chinese cohort	222 PA and 222 primary HT pts	nonalcoholic fatty liver disease prevalence higher in PA *vs* primary HT pts: 35.1 *vs* 29.7 %

Legend: CI – confidence interval; HDL-C – high-density lipoprotein cholesterol; HT – hypertension; LDL-C – low-density lipoprotein cholesterol; OR – odds ratio; PA – primary aldosteronism; TC – total cholesterol; TG – triglycerides.

Relationships between metabolic disorders and PA Subtypes, and therapy.

Data concerning differences in carbohydrate metabolism disorders between the two main PA subtypes are inconclusive. Most studies involving 50 or more PA patients reported comparable HbA1c levels and prevalence of prediabetes or DM between patients with an APA and non-lateralized PA (especially, after adjustment for age and BMI) [38,63–65]. The same is partially true for the large study by Akehi et al. discussed above, *i.e.,* for all PA cases. However, when DST-negative patients were investigated, prediabetes was more common in the non-lateralized subtype [32]. Furthermore, a 2023 *meta*-analysis of 21 studies (n = 4197 in total) showed that lateralized PA patients had significantly lower LDL-C, TC, TG, fasting glucose, HbA1c, and HOMA-IR than non-lateralized patients [66]. Since the latter usually present milder PA, cortisol may well play a more significant role than Ald in metabolic disorders.

Two retrospective studies not included in the above *meta*-analysis support this supposition. In a Chinese population, 163 lateralized and 98 non-lateralized PA patients had comparable prevalence of MetS, while a trend toward 11 % higher prevalence of IGT and DM could be observed in the latter (p = 0.07) [67]. Moreover, in Taiwanese PA patients, the presence of an APA harboring a common Ald-driving potassium channel KCNJ5 mutation, leading to severe PA was associated with fewer metabolic abnormalities than for APAs with other mutations and non-lateralized PA [68]. Overall, despite higher PA severity (more pronounced hypokalaemia, higher ARR and Ald), patients with a KCJN5 mutation-harboring APA were younger than the two latter groups (48.6 ± 10 versus 55.1 ± 11.3 and 54.3 ± 10.9), less overweight (24.7 ± 4 versus 25.1 ± 4.1 and 26 ± 3.9), less abdominally obese; MetS prevalence was lower among them: 12 % versus 21 and 63 %, respectively ($p < 0.05$). Propensity score matching of KCNJ5-positive and negative APA subjects revealed statistically significant differences in MetS prevalence, dyslipidemia (TC and TG), abdominal adiposity, Ald and kalaemia.

In another retrospective study based on the Taiwanese registry, propensity score matching indicated that the risk of new-onset DM upon a mean 5.2-year follow-up was lower in PA patients treated by adrenalectomy (n = 754), whereas higher in those treated with MRAs (n = 1613) than in patients with primary HT. The incidence rates were 28.1 for primary HT, 12.7 for adrenalectomized PA, and 34.6 thousand patient-years for MRA-treated PA [69]. Authors did associate the risk of developing DM with hyperaldosteronemia, however, cortisol cosecretion was not analyzed. In a smaller Spanish cohort (n = 648), a shorter follow-up revealed no differences in new-onset DM between the two PA treatment modalities [70]. However, again, investigating the effects of MACS is impossible: only 147 patients underwent the DST, and among 41 who tested positive just 18 underwent adrenalectomy and 12 received MRAs.

Observations similar to those from the Taiwanese cohort data were also made in a smaller study (n = 54) conducted at a Chinese center [71]. Surgery resulted in DM remission or improvement in half of lateralized diabetic PA patients; however, MACS was not investigated.

In a different approach to the question at hand, 61 nondiabetic PA patients underwent OGTT before and one year after adrenalectomy due to an APA in a Japanese study [72]. At follow-up, insulin secretion in the OGTT was higher versus baseline, whereas IR increased (despite comparable BMI and lipid levels). The latter change was suspected to result from decreased muscular blood flow due to lower BP. Overall, glucose

homeostasis was comparable at follow-up. While subjects with 1 mg DST cortisol > 82 nmol/l were excluded, this criterion is insufficient to rule out milder cortisol excess.

Different mechanisms in glucose metabolism disorders were suggested for lateralized and bilateral PA (n = 116 total) in a Japanese study: insulin secretion and sensitivity disorders, respectively [64]. Subjects with subclinical hypercortisolemia, defined as abnormal 1 mg DST combined with an additional hormonal criterion in those with cortisol < 83 nmol/l, were excluded. However, again, possible inclusion of those with milder cortisol excess limits the conclusions that can be drawn.

Finally, in a recent large (3566 PA patients) multicenter (European and Asian populations) cohort, bilateral PA cases were characterized by higher BMI and obesity prevalence than APA cases [73]. Similar to the findings mentioned above [60], female patients with bilateral PA in the multicenter cohort had a higher OR for dyslipidemia (1.75, 95 % CIL 1, 2, 2.38) and DM (3.47, 95 % CI: 1.86, 6.29) than female APA patients, despite lower 1-mg DST cortisol among the latter. DST cortisol correlated with HbA1c among APA patients, and female DST-positive APA patients had higher HbA1c than DST-negative patients. These discrepancies may stem from underpowered analyses (smaller DST-positive subgroup). A worsening of lipid profiles was also observed after surgery among female APA patients, similar to findings of the *meta*-analysis cited above [60].

With respect to other metabolic disorders, in a Korean PA cohort (n = 400), nonlateralized patients presented with higher BMI and visceral fat area (VFA) than lateralized patients did; the VFA-to-BMI ratio in the former was higher than in the latter (26.5 % among men and 50.5 % among women), *i.e.*, the milder PA subtype showed a stronger association with obesity [74]. MACS was present in as many as 31 % of male and 45 % of female PA patients but its prevalence was comparable in PA subtypes. DM was more common in male non-lateralized PA patients with (n = 12) than in those without (n = 38) MACS: 46.2 % *vs* 12 %, p = 0.046. This was not the case for lateralized PA or women.

In a retrospective cross-sectional study in a Chinese population, 84 non-lateralized and 85 lateralized PA patients were compared [75]. Again, the former exhibited a higher prevalence of MetS (79.8 % *vs* 64.7 %), obesity (40.5 % *vs* 24.7 %), and dyslipidemia (72.6 % *vs* 55.3 %) but also hyperglycemia (29.8 % *vs* 16.5 %) than did the latter. However, the prevalence of MACS was not investigated.

In light of the above (Table 4), data from a retrospective Chinese cohort indicating improved metabolic characteristics in MRA-treated PA patients (n = 51) compared to adrenalectomized patients (n = 33) are puzzling [76]. The authors admit subtype differentiation based on CT or adrenal vein sampling may have led to misdiagnosis; additionally, 90 % of the initial cohort (n = 853) was not included in the study.

Dissecting the differences in metabolic disorders between lateralized and bilateral PA affords considering possible bidirectional relationships. Obesity and MetS prevalence were repeatedly shown to be more common in bilateral than lateralized PA despite higher disorder severity in the latter [60,73–75,77]. Another study indicated the same result for visceral fat percentage [78]. Bilateral PA develops mostly due to multiple APMNs with a CACNA1D mutation, which contrasts with the common KCNJ5 Ald-driver mutation in APAs [11]. Accumulation of APMNs in morphologically normal adrenal glands occurs with aging [11]. Whether obesity-driven renin-dependent aldosteronism may eventually promote Ald autonomy remains to be elucidated. Potentially, adipocytokine secretion, insulin resistance and low-grade inflammation could be mechanistically involved in the development of bilateral PA but currently this point is unresolved [79].

Table 4
Differences in metabolic disorders between PA subtypes in selected studies.

First author, year	Study type, population	No of PA pts	Findings concerning two primary PA subtypes
Akehi, 2019 [32]	retrospective, multicenter Japanese cohort	2210 total;DST (−)/(+): 681/209	in all pts: comparable HbA1c, prediabetes and DM prevalence between PA subtypes;in DST (−) pts: prediabetes more prevalent in bilateral PA
Zhu & Zhu, 2023 [66]	*meta*-analysis	21 studies, n = 4197	lower LDL-C, TC, fasting glucose, HbA1c and HOMA-IR in lateralized *vs* bilateral PA
Bu, 2022 [67]	retrospective, single center, Chines cohort	163 unilateral, 98 bilateral	MetS comparable between PA subtypes, trend toward higher IGT and DM prevalence in bilateral PA (p = 0.07)
Chen, 2021 [68]	retrospective, Taiwanese PA registry	244 bilateral, 177 APA (incl. 102 KCNJ-5)	lower age, MetS and overweight prevalence among pts with an APA harboring a KCNJ-5 mutation compared to APAs with other mutations and pts with bilateral PA
Wu, 2017 [69]	retrospective, Taiwanese PA registry	754 treated with ADX, 1613 treated with an MRA	risk of new-onset DM by PSM (thousand patient-years): 34.6 in MRA-treated PA pts, 28.1 in primary HT pts, 12.7 in PA pts after adrenalectomy (cortisol cosecretion not reported); mean 5.2 year follow-up
Araujo-Castro, 2023 [70]	retrospective, multi-center Spanish registry	648 (ADX in 201, MRA in 269)	comparable incidence of new-onset DM between two PA treatment modalities; 31.8 (11.5–74.1)* month follow-up
Liu, 2022 [71]	retrospective, single center, Chines cohort	54 diabetic pts treated with ADX	DM remission or improvement in half of pts; MACS not investigated
Tsurutani, 2017 [72]	retrospective, single center, Japanese cohort	61 APA pts without DM	comparable glucose homeostasis in OGTT pre- and one year post-ADX but both insulinogenic index and HOMA-IR higher at follow-up: 0.8 (0.7–1.1) *vs* 0.5 (0.4–0.8)*, and 1 (0.6–1.5) to 1.5 (1–2.2)*, respectively
Okazaki-Hada, 2020 [64]	retrospective, single center, Japanese cohort	116 (28 APA)	disorders of insulin secretion in lateralized and insulin resistance in bilateral PA; pts with DST cortisol < 83 nmol/l included in the study
Spyroglou, 2022 [73]	multi-center Asian and European cohort	3566 (1:1 APA-to-bilateral PA ratio)	higher BMI and obesity prevalence in bilateral PA; female pts with bilateral PA had higher OR for dyslipidemia and DM but lower DST cortisol compared to APA pts; HbA1c correlated with DST cortisol in APA and was higher in DST(+) *vs* (−) female pts

(*continued on next page*)

Metabolic disorders and outcomes of adrenalectomy

Metabolic disorders have been found to predict the absence or partial surgical cure of PA. In another 2022 *meta*-analysis by Manosroi et al. including 32 studies with 5601 PA patients, clinical success was

Table 4 (*continued*)

First author, year	Study type, population	No of PA pts	Findings concerning two primary PA subtypes
Park, 2024 [74]	retrospective, single center, Korean cohort	400 (268 lateralized, 132 bilateral)	bilateral PA associated with obesity (higher BMI and VFA-to-BMI ratio); MACS present in 31 % of male and 45 % of female pts with comparable prevalence between subtypes
Zhang, 2021 [75]	retrospective, single center, Chinese cohort	84 bilateral, 85 lateralized	bilateral pts had higher prevalence of MetS, obesity, dyslipidemia, hyperglycemia; MACS not investigated

Legend: * medians and interquartile ranges; ADX – adrenalectomy; APA – aldosterone-producing adenoma; BMI – body mass index; DM – diabetes mellitus; DST – 1-mg overnight dexamethasone suppression test; HbA1c – glycated hemoglobin; HOMA-IR – homeostasis model assessment-insulin resistance index; HT – hypertension; IGT – impaired glucose tolerance; ISI – insulin secretion index; LDL-C – LDL cholesterol; MACS – mild autonomous cortisol secretion; MetS – metabolic syndrome; no – number; MRA – mineralocorticoid-receptor antagonist; OGTT – oral glucose tolerance test; OR – odds ratio; PA – primary aldosteronism; PSM – propensity-score matching; pts –patients; TC – total cholesterol; VFA – visceral fat amount; *vs* – versus.

predicted by lower BMI in 17 studies (with a standardized mean difference of −0.49, 95 % CI: −0.58′-0.39), lower incidence of DM in nine studies (OR 0.36, 95 % CI: 0.22; 0.59) and lower incidence of dyslipidemia in three studies (OR 0.29, 95 % CI: 0.15; 0.58) [80]. PA cure was defined as per PA surgical outcomes (PASO) criteria or as normotension without hypotensive medications [81].

Findings from individual reports not included in the *meta*-analysis were similar: in a 2021 two-center Singapore study, absence of clinical cure was associated with hyperlipidemia and DM at 6–12 months post-surgery [82]; data from the Spanish PA registry revealed that negative factors for HT resolution upon surgery included both DM (n = 156) and obesity (same study as for DM, and n = 415 in a separate study) [83,84], which was also the case for a complete clinical cure in a Tunisian study (n = 71) [85]. Again, BMI ≥ 25 and DM were found to predict persistent HT post-surgery in 353 Chinese PA [86]. These studies applied the PASO criteria to define outcomes. Finally, a multivariate analysis revealed that BMI, DM and dyslipidemia, treated as one variable (MetS-related disease), were negative predictors of clinical success (defined as normotension without hypotensive medications) after adrenalectomy in a Japanese cohort (n = 71) [87].

Importantly, in light of the discussion above, neither the original studies nor the 2022 *meta*-analysis investigated cortisol cosecretion. Therefore, this aspect of the discussion of metabolic disorders in the course of PA requires further clarification.

Summary and conclusions

Multiple mechanisms, including hypokalaemia, have been proposed to explain the increased prevalence of DM and obesity of PA patients compared with primary HT patients [88]. However, this review questions causative relationships between Ald and metabolic disorders in PA, since studies incorporating assessment of autonomous cortisol cosecretion point to glucocorticoids as culprit factors for DM/prediabetes and overweight/obesity. In brief, 1) the prevalence of DM and MetS is increased in PA patients compared with primary HT patients overall, but excluding MACS from the first group makes the rates comparable; 2) patients with a less severe (non-lateralized) PA subtype present with more pronounced metabolic disorders; 3) the significance of glucocorticoid cosecretion in the course of PA may not be sufficiently captured with the 1-mg DST test (24-h urinary total glucocorticoid metabolites output possibly provides a better measure). Factors further complicating definitive conclusions include the lack (or scarcity) of data on glucocorticoid autonomy in studies investigating post-surgical metabolic outcomes in lateralized PA, and the fact that PA patients have less pronounced dyslipidemia compared with primary HT patients.

In a recent study of patients grouped according to the following diagnoses: primary HT, PA, pheochromocytoma and Cushing's syndrome, a comparison of the first two groups revealed that Ald was not associated with most metabolomic differences [58]. In fact, associations were more significant for cortisone, cortisol and DHEA in order of decreasing importance. Carbohydrate dysmetabolism and the MetS phenotype were shown to depend mainly on cosecreted steroids and not Ald itself. An argument for glucocorticoids carrying their deleterious effects in the Ald autonomy spectrum was mentioned above for osteoporosis in one study with possible AAS cases. While PA has been suggested as a secondary cause of osteoporosis [89], the situation may be analogous to findings for DM in PA.

Clearly, further studies are needed to elucidate the roles of Ald, cortisol and other adrenal steroids in metabolic disorders in the course of PA. However, at this point, previously suspected associations between the mineralocorticoid and DM or overweight/obesity must be reviewed. Data on AAS /mild PA are scarce, and further research concerning the entirety of the PA spectrum should incorporate the assessment of possible glucocorticoid cosecretion.

CRediT authorship contribution statement

Piotr Kmieć: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Renata Świątkowska-Stodulska:** Writing – review & editing, Supervision.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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