Review

Primary aldosteronism: an unsuspected culprit of hypertension in systemic lupus erythematosus?

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ABSTRACT

Primary aldosteronism (PA) is the most common endocrine cause of secondary hypertension and is associated with a high risk of cardiovascular disease in the general population. Patients suffering from systemic lupus erythematosus (SLE), a multisystem and multifactorial autoimmune disease, experience a high burden of hypertension and cardiovascular disease. Importantly, cardiovascular disease is one of the leading causes of death in SLE. Very limited evidence suggests an increased proportion of autoimmune diseases such as SLE in patients with PA. However, studies evaluating the prevalence of PA in the SLE population are lacking. Despite the potential for curative or targeted treatments, guidelines for the management of hypertension in SLE do not currently recommend testing for PA. This review highlights PA as a potentially overlooked secondary cause of hypertension in SLE, and offers future directions in research to improve the detection of this highly modifiable cardiovascular risk factor in the SLE population.

Introduction

Primary aldosteronism (PA) is the most common endocrine cause of secondary hypertension (1). It is characterised by autonomous aldosterone production by the adrenal gland resulting in a low or suppressed plasma renin (1, 2). Studies over the past decade have reported prevalence estimates of PA between 5–14% of hypertensive patients in primary care and up to 30% in those with resistant hypertension (3-8). Compared with essential hypertension, aldosterone-mediated hypertension is associated with a higher risk of cardiovascular complications including heart failure, myocardial infarction, arrhythmias, and stroke (9). Despite this, PA remains largely under-diagnosed (10), resulting in the under-utilisation of available targeted therapies or surgical cure, both of which could reduce the PA-associated cardiovascular risk (9).

People suffering from systemic lupus erythematosus (SLE), a multifactorial and multisystem autoimmune disease (11), frequently develop cardiovascular disease with increased cardiovascular mortality, and with hypertension being a significant contributor (12). Furthermore, patients with SLE are more likely to suffer from hypertension compared to those without SLE. Despite reports of a prevalence ranging between 9 and 77%, the mechanisms underlying hypertension in SLE remain poorly understood (12). It has been hypothesised that renal and chronic systemic inflammation, autoantibodies, pro-inflammatory cytokines and glucocorticoid therapy may contribute to the development of hypertension in SLE (13).

There is very limited published evidence for an association between PA and SLE. A recent study of patients with hypertension without a previous diagnosis of an autoimmune disease found a significantly higher incidence of new onset autoimmune disease in patients with PA compared to matched patients with essential hypertension (14). To the best of our knowledge, the prevalence of PA in patients with SLE has not yet been evaluated. At present, screening for PA is not included in management guidelines for hypertension in patients with SLE or lupus nephritis (15, 16).

In this review, we explore the cardiovascular factors that contribute to morbidity and mortality in patients with SLE, examine the potential role of aldosterone excess in the pathophysiology of hypertension and cardiovascular

disease, and highlight gaps in the understanding of and recommendation for the diagnosis and management of PA in people with SLE.

Hypertension: the leading risk factor for cardiovascular disease in SLE

People with SLE are at increased risk of cardiovascular disease and its complications compared to the general population, with studies reporting an 2.6-3 fold increase in incidence of acute myocardial infarction (17, 18) although one study found a 50-fold greater risk of acute myocardial infarction in patients aged 35–44 years (19). Similarly, risk of stroke and cardiovascular disease is increased, with adjusted multivariate hazard ratios for patients with SLE being 2.14 (95% CI 1.64–2.79) and 2.28 (95% 1.9–2.73), respectively (18), and there is a reported 2-3-fold increase in cardiovascular mortality, increasing to 16-fold in patients with SLE aged 20–39 years (18, 20-22).

Hypertension, defined as systolic blood pressure (SBP) of ≥130 mm Hg and/or diastolic BP (DBP) of ≥80 mm Hg (23), is much more prevalent in SLE than in the general population, reported to be as high as 77%, though this varies greatly (12). Hypertension is independently associated with the accrual of irreversible end-organ damage and atherosclerotic vascular events in patients with SLE (24-31). Additionally, recent cross-sectional studies report that one quarter to two thirds of patients with SLE receiving antihypertensive medications have sub-optimal blood pressure control (32, 33). Nocturnal hypertension and loss of day-night BP dipping is more common in patients with SLE compared with controls, and present in more than 50% of patients with active lupus nephritis (34-36). Resistant hypertension, variably defined in studies as elevated BP despite concurrent use of at least three or four different classes antihypertensives to achieve BP targets, was nearly twice as prevalent in patients with SLE compared to their controls (hazard ratio [HR] 1.7; 95% confidence intervals (CI) 1.28–2.30) (37-39). Therefore, the effective management of hypertension is an important modifiable aspect of the care of patients with SLE, with implications for both quality of life and mortality (19).

Pathophysiology of hypertensionin SLE

The pathophysiology of hypertension in SLE has been attributed to several factors (Fig. 1). Given the high prevalence of nephritis in SLE (approximately 40% of patients), many have chronic kidney disease (CKD); reduced glomerular filtration rate leading to abnormal pressure natriuresis is thought to play a central role in the development of high BP (40, 41). Renal injury in lupus nephritis is initiated by the deposition of immunoglobulins and complement activation in the glomerular subendothelial and subepithelial spaces (42) (43). Subsequent leucocyte infiltration and inflammatory cytokine production is believed to disrupt cell-cell interactions, promote microvascular endothelial cell and basement membrane injury as well as mesangial cell proliferation, while impairing vascular function, thereby contributing to systemic hypertension. When inflammation is persistent or severe, glomerulosclerosis and tubulointerstitial fibrosis ensues. Tubulointerstitial injury is common in lupus nephritis, exacerbating renal haemodynamic changes, with moderate to severe interstitial fibrosis and tubular atrophy being associated with hypertension and subsequent progression to end stage renal failure (44, 45). Patients with SLE may also have other systemic metabolic conditions, such as obesity and diabetes mellitus, that themselves can promote the development of CKD through non-immune mechanisms (46).

Vascular endothelial dysfunction in SLE, compounded by circulating autoantibodies and inflammatory mediators, has also been proposed to contribute to hypertension, though this relationship is unclear (47-50). Additionally, an activated renin-angiotensin system contributes to hypertension in SLE, supported by elevated plasma levels of angiotensin-converting enzyme (ACE) and renin in some patients with SLE with reduced renal function and by the efficacy of ACE inhibitors (ACEI) and angiotensin receptor blockers (ARBS) in blood pressure control in this patient group (51-56). There is also evidence to suggest that people with SLE are more likely to have an overactive sympathetic nervous system, with studies identifying significantly elevated levels of a norepinephrine degradation metabolite, plasma 3-methoxy-4-hydroxyphenylglycol, and adrenal chromogranin A, indicating sympathetic nervous system hyperactivity (57, 58). Other suggested contributing factors include oxidative stress mediating impaired renal haemodynamics, pro-inflammatory cytokines increasing risk of metabolic syndrome and endothelial injury mediated by antiphospholipid antibodies (48, 59-62).

While there are several guidelines available for the assessment and management of hypertension, none are specific for patients with SLE (63-67). Hence, recommendations for the investigation and management of hypertension in patients with SLE is similar to advice for that given to the general hypertensive population. However, whilst PA is recognised as a common cause of secondary hypertension generally in the hypertensive population, it has not been discussed as a potential cause of hypertension and heighted cardiovascular risk in SLE (15, 16, 68).

Pathophysiology of PA: an unsuspected contributor to hypertension

PA is the most common endocrine cause of secondary hypertension and is associated with a high risk of cardiovascular disease in the general population. Aldosterone is a steroid hormone, produced by the adrenal cortex, which acts via the mineralocorticoid receptors (MR) in the distal convoluted tubule and collecting ducts of the kidney to promote sodium reabsorption, increase potassium excretion and regulate BP (69). In PA, aldosterone is autonomously produced from either adenomatous or hyperplastic adrenal tissue, independent of its normal regulators such as renin and potassium (70, 71). High levels of aldosterone lead to inappropriate sodium resorption, coupled with potassium and hydrogen release (72). This contributes to extracellular volume expansion and hypertension, with

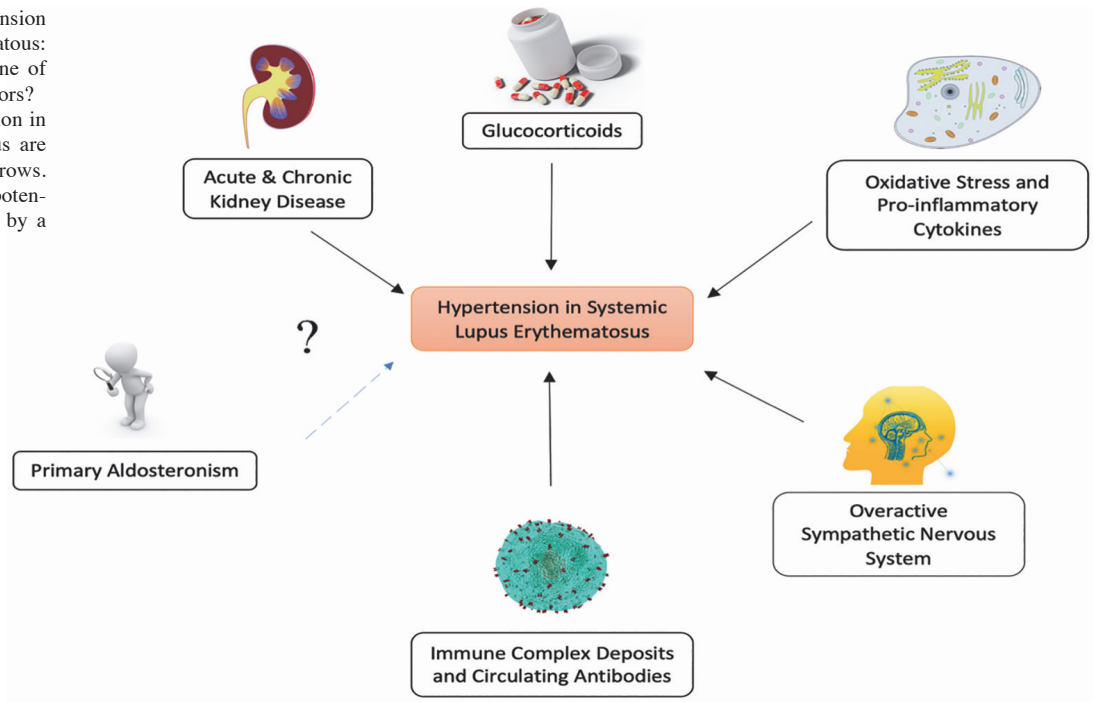

Fig. 1. Aetiology of hypertension in systemic lupus erythematous: primary aldosteronism as one of the many potential contributors? Known causes of hypertension in systemic lupus erythematous are indicated by solid black arrows. Primary aldosteronism as a potential contributor is indicated by a dotted black arrow.

hypokalaemia and metabolic alkalosis in some cases (71).

Patients with PA usually present with hypertension and are found to have low or suppressed renin together with normal or elevated aldosterone concentration, while hypokalaemia is not a common feature for a majority of them (73). Importantly, aldosterone excess affects more than just salt and water (Fig. 2). The inappropriate activation of the MR impacts a range of cell types, including cardiomyocytes, endothelial cells and immune cells, and causes tissue inflammation, fibrosis and endothelial dysfunction, with clinical consequences detailed in later parts of this review (74).

Detection and prevalence of PA

Screening for PA involves measuring the plasma aldosterone to renin ratio (ARR) which is considered positive when elevated above a laboratory-specific threshold (ranging between 50–100 pmol/L:mU/L). Patients with a positive screening test require confirmatory testing which involves manoeuvres to suppress aldosterone, that may include fludrocortisone administration, intravenous saline infusion, oral salt loading or captopril challenge (70, 75). The lack of adequate aldosterone suppression in response to one of these interventions is considered diagnostic of PA.

PA is a common condition worldwide. It accounts for 5–14% of patients with hypertension in primary care and up to 30% of those who have been referred for specialist management, making it one of the most common causes of secondary hypertension (1, 10, 76). A prospective Italian study found an overall prevalence of 5.9% in 1,672 hypertensive patients recruited from primary care which included a prevalence of 3.9% in stage 1 (SBP 130–139 mm Hg or DBP 80–89 mm Hg), 9.7% in stage 2 (SBP ≥ 140 mm Hg or DBP ≥90 mm Hg) and 20% in resistant hypertension (6, 77). In a similar study in China, of 1,020 patients with newly diagnosed hypertension screened over 16 months, at least 4% were confirmed to have PA while an additional 3% were considered likely to have PA (8). In Australia, a general practitioner-led screening study identified PA in 14% of 247 treatment-naive hypertensive patients (10).

The real-world prevalence, however, differs substantially given the overall lack of screening for PA. A population-based cohort study conducted in Canada investigated 1.1 million adults with hypertension between 2012 and 2019 (78). Only 7,941 people (0.7%) were screened for PA and of those screened, 1,730 (21.4%) received tests results consistent with a diagnosis of PA (78). In a multi-centre study of CKD clinics, 39% of 600 patients had a guideline-recommended indication for PA testing but only 14% of those eligible were actually screened (79). The data suggest that the prevalence of PA may be underestimated by the low rates of screening. Even in patients with features highly suggestive of PA, such as those with resistant hypertension or hypokalaemia, only 2.1% (97 of 4,660 patients) and 1.6% (422 of 26 533 patients) were respectively screened for PA (78, 80).

The importance of diagnosing PA

PA is important to diagnose because it confers a higher risk of cardiovascular and renal complications than BP-matched essential hypertension. A systemic review and meta-analysis, conducted on 3,838 patients with PA and 9,284 patients with essential hypertension from 31 studies, reported that patients with PA had a significantly increased risk of stroke (odds ratio (OR) 2.58; 95% CI 1.93–3.45), coronary artery disease (OR 1.77; 95% CI 1.10–2.83), atrial fibrillation (OR 3.52; 95% CI 2.06–5.99), and heart failure (OR 2.05; 95% CI 1.11–3.78) compared to those with essential hypertension (81). A heightened risk of cardiovascular events was observed in 1,433 hypertensive people with renin-independent

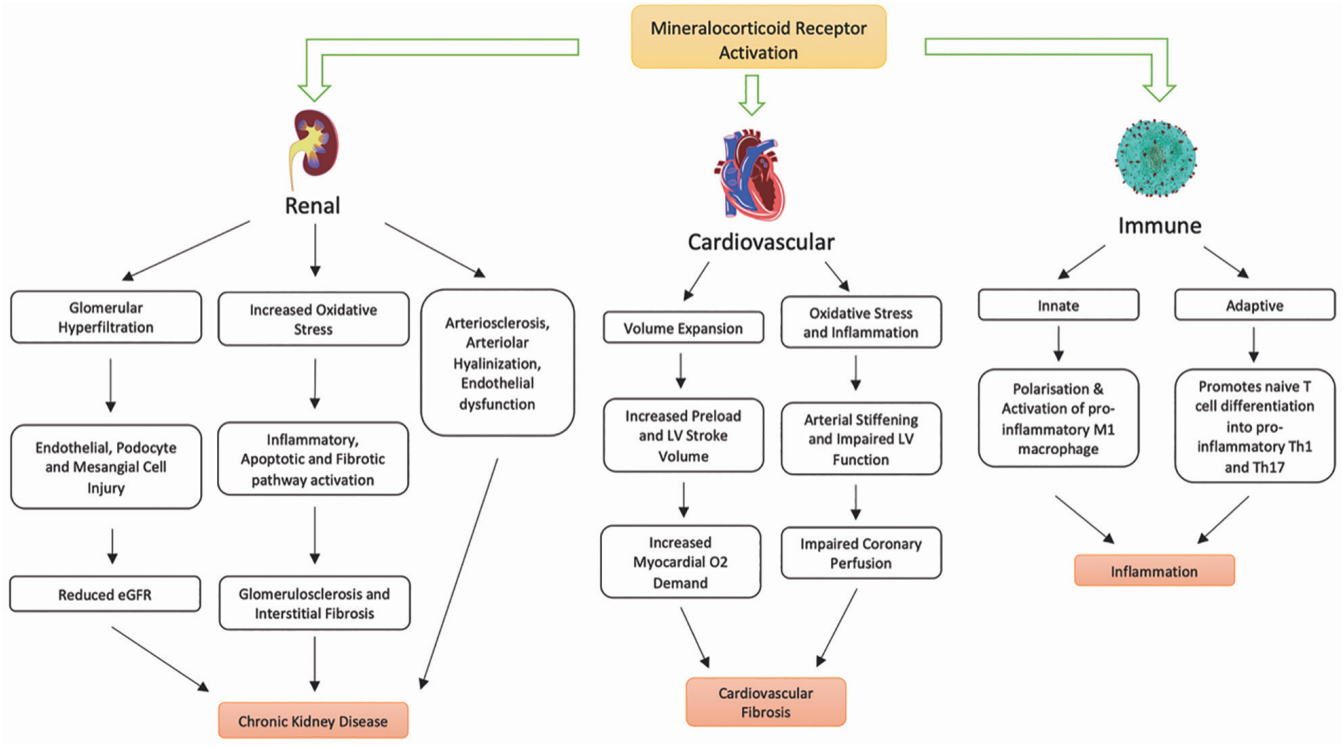

Fig. 2. Primary aldosteronism and the multi-system consequences of mineralocorticoid receptor activation.
Activation of the mineralocorticoid receptor in a range of tissue types lead to downstream effects that contribute to the pathogenesis of chronic kidney disease, cardiovascular fibrosis and inflammation. Th1: T helper 1 cells; Th17: T helper 17 cells.

aldosteronism, even without a formal diagnosis of PA (hazard ratio 1.40; 95% CI 1.08–1.82), compared to hypertensive patients with normal aldosterone levels (82). The deleterious effect of aldosterone excess on the kidney was reported by another systematic review and meta-analysis of 46 studies with 6,056 patients with PA and 9,733 patients with primary hypertension, which showed that PA was significantly associated with microalbuminuria (OR 2.09; 95% CI 1.40–3.12) and proteinuria (OR 2.68; 95% CI 1.89–3.79), and an increased estimated glomerular filtration rate (by 4.59ml/min; 95% CI 1.37–7.81), indicative of glomerular hyperfiltration (83).

Importantly, these complications can be prevented or ameliorated with targeted treatment. In those with unilateral adrenal disease, laparoscopic adrenalectomy can lead to complete cure of hyperaldosteronism (defined as the normalisation of aldosterone to renin ratio and potassium concentration) and normalisation of cardiovascular risk (84-86). In a retrospective case series of 705 patients from 12 centres worldwide, 94% achieved complete cure of their hyperaldosteronism following surgical management, and 84% had either complete normalisation of their BP or improvement in BP control (87). In patients with bilateral adrenal disease, a MR antagonist (MRA) therapy (usually spironolactone) is ideal for controlling BP and blocking aldosterone-mediated adverse tissue effects (84, 86), thereby leading to a reduction in cardiovascular risk. In a large retrospective cohort study of 602 patients with PA and 41,853 age-matched patients with essential hypertension, excess risk for cardiovascular events and mortality was observed in patients with bilateral PA whose renin activity remained suppressed, indicating inadequate dosing of MRA (adjusted HR 2.83 [95% CI 2.11–3.80], and 1.79 [1.14–2.80], respectively). In contrast, patients with PA who had unsuppressed renin, indicating adequate treatment of aldosterone excess, had no excess risk (86).

PA, autoimmunity and SLE

It has been proposed that PA may have an autoimmune basis, although evidence supporting this is limited at present. Serum levels of autoantibodies against angiotensin II type 1 receptor (AT1R), named AT1R-AA, have been found significantly elevated in PA patients who have aldosterone-producing adenomas compared to normotensive patients (88). These autoantibodies activate AT1R and cause production of aldosterone in adrenal cells (89). However, AT1R-AA were not detected in all PA patients and have also been reported in other hypertensive disorders such as preeclampsia, malignant hypertension and renal transplantation (90, 91) and thus their specificity for PA is uncertain.

PA has been investigated for its association with the development of new onset autoimmune diseases. From Taiwan's National Health Insurance Research Database from 1997 to 2009, 2,319 patients with PA without a prior diagnosis of an autoimmune disease were matched with 9,276 patients with essential hypertension (14). It was found that the incidence of a new autoimmune disease was higher in PA patients with a hazard ratio of 3.82 (14). There have also been case reports of patients with both PA and autoimmune thyroid diseases such as Grave's and Hashimoto's thyroiditis (92, 93). However, these

studies have been observational and could not explore a potential pathophysiological link between PA and autoimmune diseases (92, 93).

There is some data to suggest that MR antagonism may be immunomodulatory in autoimmune diseases. When lupus-prone NZB/W F1 female mice were administered spironolactone or placebo, spironolactone treatment resulted in lower serum anti-dsDNA levels, milder histological features of glomerulonephritis, with less proteinuria and reduced intra-renal gene expression of pro-apoptotic genes and pro-inflammatory cytokines, including interferon (IFN)-γ and B lymphocyte stimulator (94). This suggests that MR antagonism may modulate autoimmunity and intra-renal inflammation in lupus nephritis. In 21 patients with rheumatoid arthritis and other forms of inflammatory arthritis, 76% of patients receiving spironolactone had improvement in their disease activity (95). Additionally, *in vitro* spironolactone-treated, lipopolysaccharide- and phytohaemoglutinin-P-stimulated human mononuclear cells demonstrated significant inhibition in gene expression of pro-inflammatory cytokines, including IFN-γ and tumour necrosis factor (95).

Unexplored prevalence of PA in SLE

According to the 2017 American College of Cardiology/American Heart Association hypertension guidelines, PA screening is recommended in high-risk populations including patients with resistant hypertension (96). Given the higher prevalence of resistant hypertension in SLE and the potential link between the immunomodulatory effects of hyperaldosteronism and higher incidence of autoimmune disease, it could be argued that patients with HT and SLE should be screened for PA (37). Previous reviews have explored the prevalence and mechanisms of hypertension in patients with SLE, without specific reference to PA as a potential cause (12, 13, 97). Some SLE guidelines, such as the European Alliance of Associations for Rheumatology (EULAR), American College of Rheumatology (ACR) and Kidney Disease Improving Global Outcomes (KDIGO) guidelines for lupus nephritis management, refer to treating hypertension in lupus nephritis, however they do not mention PA screening (15, 16, 68). The lack of guideline recommendation for PA screening may be due to the assumption that renal disease in SLE is sufficient to explain the high prevalence of hypertension in this population and the lack of evidence to recommend broad screening for endocrine hypertension in patients with SLE.

PA may compound cardiovascular and renal complications of SLE

The accurate diagnosis of PA in patients with SLE may be particularly important as aldosterone-mediated cardiovascular and renal complications may compound end-organ injury in SLE. Patients with SLE are already at a higher risk of cardiovascular and renal complications, such as ischaemic heart disease, stroke, and CKD, given the accelerated atherosclerotic process that occurs in SLE. However, this may be further exacerbated by higher levels of aldosterone, known to promote cardiac fibrosis, cell death and hypertrophy (55, 56, 98-101), and remodelling of renal vessels, tubulointerstitial fibrosis and glomerular injury with ongoing inflammation and reactive oxidative species (99). In the absence of studies that directly evaluate plasma aldosterone concentration in people with SLE, inferences can be drawn from population-based studies which demonstrate increased risk of cardiovascular mortality in people with higher plasma aldosterone. In the Ludwigshafen Risk and Cardiovascular Health (LURIC) study of 3,153 people who had previously undergone coronary angiography, those with aldosterone concentration in the highest quartile had a hazard ratio of 1.63 (95% CI 1.20–2.20) for cardiovascular mortality (102). The association between higher plasma aldosterone concentration and cardiovascular mortality as well as sudden cardiac death was strongest in those with lower renal function (103). Analysis of the Framingham Offspring Study also found that people with hypertension and higher aldosterone concentration independent of renin (a phenotype that resembles PA) had a higher risk of cardiovascular disease with a hazard ratio of 1.40 (95% CI 1.08–1.82) (82). In keeping with the findings of these population studies, higher plasma aldosterone levels in 356 patients presenting with ST-elevation myocardial infarction were significantly associated with increased rates of in-hospital death, cardiovascular death, heart failure, ventricular fibrillation, and resuscitated cardiac arrest; furthermore, those with higher plasma aldosterone had increased mortality 6 months later (104). Beyond the effects on cardiovascular disease and mortality, plasma aldosterone concentration has also been found to be associated with CKD (OR 1.39; 95% CI 1.22–1.60) (105), albuminuria (106), and reduced glomerular filtration rate (107). Overall, the data suggests that in patients with SLE, concurrent aldosterone excess may compound the end-organ damage that they already experience.

In patients with SLE and PA, the benefits of MRA treatment will likely extend beyond BP control to additional protection against MR-mediated cardiovascular and renal injury (108, 109). A series of landmark randomised clinical trials have shown that currently available steroidal MRA (spironolactone and eplerenone) reduce mortality and hospitalisations in patients with heart failure (110-112). Patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure treated with eplerenone in addition to optimal medical therapy had a reduction in rates of death or hospitalisations related to cardiovascular causes (relative risk [RR] 0.87; 95% CI 0.79–0.95), and sudden death from cardiac causes (RR 0.79; 95% CI 0.64–0.97) (117). More recent clinical trials of a non-steroidal MRA (finerenone) have also demonstrated risk reduction in cardiovascular and renal events in patients with type 2 diabetes mellitus and CKD, including those with pre-existing heart failure or cardiovascular disease (113-115). Patients with CKD, elevated albuminuria and type 2 diabetes who were treated with finerenone, showed a reduction in cardiovascular death, as well as non-fatal myocardial infarc-

Table I. Medications interfering with PA screening relevant to SLE management.

Class	Drug examples	Mechanism of action	Effect on plasma levels		ARR
			Aldosterone	Renin	
ACEI	perindopril ramipril enalapril fosinopril lisinopril	Block angiotensin-converting enzyme that converts angiotensin I to angiotensin II, decreasing vasoconstriction of arteries, enhancing natriuresis	↓	↑	FN
ARB	candesartan irbesartan olmesartan valsartan telmisartan	Block the binding of angiotensin II to angiotensin 1AT1 receptors, inhibited angiotensin II effect	↓	↑	FN
MRA	spironolactone eplerenone	Binds to the mineralocorticoid receptor, inhibiting effects of aldosterone, increasing natriuresis	↑	↑	FN
Beta blocker	atenolol metoprolol	Inhibited catecholamine binding to beta receptors, resulting in a negative inotropic effect	↓	↓	FP
Calcium channel blocker (dihydro-pyridine)	amlodipine felodipine nifedipine lercanidipine	Inhibits calcium ions entry to cells by binding to L-type voltage gated calcium channels, resulting in peripheral vasodilation	↓	↑	FN
Diuretic	Loop acting (frusemide)	Inhibit Na/K/Cl transporter in thick ascending limb of Loop of Henle, increasing sodium excretion	↑	↑	FN
	Thiazide (hydrochlorothiazide, chlorthalidone)	Blocks Na/Cl channels, inhibited sodium transport in distal tubule resulting in natriuresis	↑	↑	FN
	Potassium sparing (amiloride)	Blocks epithelial sodium channels in distal tubule, inhibiting sodium reabsorption	↑	↑	FN
Alpha-2 agonist	methyldopa	Agonist effect on alpha-2 adrenergic receptors, reducing vasoconstriction	↓	↓	FP
NSAID	Cox 1 and 2 inhibitors (ibuprofen, indomethacin)	Inhibit enzyme cyclooxygenase, inhibiting prostaglandin production	↓	↓	FP
	Selective Cox 2 inhibitors (celecoxib, meloxicam)	Selectively inhibit enzyme cyclooxygenase 2, inhibiting prostaglandin production	↓	↓	FP

ACEI; angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker; ARR: aldosterone to renin ratio; FN: false negative; FP: false positive; MRA: mineralocorticoid receptors antagonists; NSAID: non-steroidal anti-inflammatory drug.
↑ increase concentration; ↓ decrease concentration.

tion, non-fatal stroke or hospitalisation from heart failure (hazard ratio 0.87; 95% 0.76–0.98) (108). Experimentally, in renal ischaemia reperfusion injury (IRI) in the rat, both spironolactone and finerenone treatment prior to IRI protected rats against acute kidney injury, mediated by a reduction in oxidative stress, and the subsequent development of renal fibrosis and CKD (109, 116). Furthermore, MRA has been shown to attenuate vascular calcification induced by glucocorticoid activation or CKD (117-119). Overall, patients with SLE who also have PA are likely to experience a greater degree of cardiovascular and renal damage which may be ameliorated by targeted treatment of PA.

Challenges of PA screening in patients with SLE

As hypertension is prevalent in people with SLE, many patients take one or more antihypertensive agents (120). Despite this, it is estimated that 24.4 to 48% of patients with SLE have a BP of greater than 140/90 mm Hg (33, 121, 122). A Canadian study reported that the most commonly used medications are ARB, followed by calcium channel blockers (CCB), diuretics, ACEI and beta-blockers (BB) in 108 patients with SLE currently on antihypertensive medications, with 38 of these taking multiple medications concurrently (33). Aside from control of hypertension, antihypertensive use is further incentivised by their additional renal and cardiovascular protection, as well as other therapeutic uses, such as CCB for Raynaud's phenomenon, a common manifestation of SLE (120, 123).

Whilst these antihypertensives medications are helpful in SLE, they can interfere with PA screening by affecting aldosterone and/or renin concentration, resulting in false negative or positive ARR results (70) (Table I). It is recommended that interfering medications be stopped for 4–6 weeks prior to measuring ARR, when safe to do so (70, 124). BP can be managed by non-interfering medications including sustained-release verapamil, prazosin, moxonidine and/or hydralazine (124-127). However,

cessation and replacement with other antihypertensive can result in adverse effects, including significant increases in BP and severe hypokalaemia (125). There may also be hesitancy to change medications given comorbidities, especially cardiovascular disease, in patients with SLE. Hence, if the ARR is measured whilst the patient is taking interfering medications, the results should be interpreted accordingly (124).

There are other complicating medications, such as glucocorticoids and NSAID, used by up to 80% of patients with SLE (128, 129), that can interfere with the interpretation of aldosterone and renin concentrations (Table I). Glucocorticoids such as prednisolone can also activate the mineralocorticoid receptor at high does (≥50mg/day) and therefore cause sodium and water retention, leading to a suppressed renin concentration and potentially false positive ARR (130, 131).

Additionally, aldosterone and renin levels may be difficult to interpret in patients with renal impairment. As creatinine clearance declines, aldosterone metabolites can accumulate and falsely increase the plasma aldosterone level (if measured using immunoassay) while renin secretion decreases, potentially leading to false positive results (132-135). The increasing use of liquid chromatography-tandem mass spectrometry to measure aldosterone independent of related steroid metabolites provides a more accurate measure in the setting of renal impairment.

These barriers to the accurate detection of PA are important to consider in SLE where 40% of patients will develop lupus nephritis, of whom 10% will develop end-stage kidney disease (136). All of these challenges can be overcome by screening for PA as early as possible in patients with SLE and hypertension, prior to the initiation of antihypertensives and the development of CKD.

Conclusion

PA is a common and important cause of hypertension that is not routinely sought in patients with SLE, despite the high prevalence of hypertension in this population group. An accurate diagnosis is important as PA is potentially curable or has effective targeted treatments, but left untreated, it can exacerbate cardiovascular and renal injury which already affects many patients with SLE. If PA is indeed a common contributor to hypertension and cardiovascular complications in SLE, then targeted treatment with MRA or laparoscopic adrenalectomy could improve BP control using fewer medications, reduce cardiovascular risk, prevent aldosterone-mediated tissue injury and improve patients' quality of life. It is important to highlight that MRA could provide additional cardiac and reno-protective benefits in patients with SLE. Current barriers include the difficulties in interpreting aldosterone and renin levels in the settings of renal disease and interfering medications. We propose that PA should be screened in the initial assessment of hypertension in patients with SLE, especially in patients who are yet to start antihypertensive medications, so that the condition can be accurately detected in a timely manner and cardiovascular-renal complications can be prevented. Patients with features highly suggestive of PA, such as resistant hypertension or hypokalaemia, should also be tested although the empiric use of MRA may be a pragmatic solution in circumstances where PA testing is not feasible.

Key messages

- Patients suffering from SLE experience a high burden of hypertension and cardiovascular disease.
- Primary aldosteronism, the commonest endocrine cause of hypertension, is associated with high cardiovascular disease risk.
- Primary aldosteronism is a neglected but potentially highly relevant cause of hypertension in SLE patients.

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