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Review

Systemic lupus erythematosus and hypertension

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ABSTRACT

Systemic lupus erythematosus (SLE) is associated with a high burden of cardiovascular disease (CVD), which is in part imputed to classical vascular risk factors such as hypertension. Hypertension is frequent among patients with SLE and studies show it is more prevalent in SLE patients than in people without SLE. Despite the high frequency of hypertension in SLE patients, the pathophysiological mechanisms underlying the development of hypertension remain poorly understood. 24-h ambulatory blood pressure monitoring has emerged as a valuable tool in determining blood pressure (BP) in SLE patients in whom hypertension has been associated with damage accrual, stroke and cognitive dysfunction. Although prevalent, current guidelines neglect the specific management of hypertension in SLE patients in their recommendations. This review discusses the mechanisms that may lead to hypertension and the literature evaluating hypertension screening and management in SLE patients.

1. Introduction

Although there is still no definitive treatment for systemic lupus erythematosus (SLE), the introduction of corticosteroids and immunosuppressants has resulted in a significant modification in its natural history. However, the number of complications associated with chronic treatment with these drugs has also increased. Treatment with corticosteroids, immunosuppressants, and non-steroidal anti-inflammatory drugs, widely used for the control of inflammatory symptoms, may cause, among other complications, BP elevation or the worsening of existing essential hypertension, which may have deleterious health effects. Renal disease, which occurs in the natural evolution of some systemic autoimmune diseases, may also result in secondary arterial hypertension.

SLE patients have a 5–6 fold increase in the risk of a cardiovascular event and a 50-fold greater risk of acute myocardial infarction when compared with the age-matched general population [1].

Several factors have been shown to be relevant to this increased risk. Both traditional and SLE-related factors, such as systemic inflammation and potential therapies administrated for SLE could contribute to this increased cardiovascular risk [2]. As mentioned, hypertension is one of the most relevant modifiable factors involved in the development of atherosclerosis and cardiovascular diseases (CVD) in SLE patients [3].

The prevalence of hypertension in SLE is reported to vary greatly, reaching 77% in some cohorts (Table 1). Compared with SLE patients, the prevalence of hypertension in controls without lupus is significantly lower, and is reported to reach 7.7% in those aged 22–44 years [4].

This study reviews the literature pertaining to the evaluation and management of hypertension in SLE patients.

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† Dr. Alejandro Ruiz-Argüelles died on 25 July 2019. This work is dedicated to the memory of Dr. Ruiz-Argüelles, a coauthor of this review article.

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Table 1
Studies of hypertension prevalence in SLE patients and controls.

Reference	Hypertension definition	Group	Number	Age (years)	Female (%)	GC, n (%)	Hypertension (%)
Bruce et al. [79]	≥140/90 mmHg or anti-HT	SLE	250	45	100	55	33.0
		Control	250	44	100		13.0
Zhang et al. [44]	≥140/90 mmHg or anti-HT	SLE	111	34	100	100	29.7
		Control	40	34	100		2.5
Bellomio et al. [80]	≥130/85 mmHg or anti-HT	SLE	149	37	89	NR	43.0
		Control	117	43	86		25.0
De Leeuw et al. [81]	≥140/90 mmHg or anti-HT	SLE	74	37	85	45	31.0
		Control	74	38	89		7.0
Nienhuis et al. [82]	≥140/90 mmHg or anti-HT	SLE[b]	30	42	87	63	30.0
		Control	30	41	87		0.0
Santos et al. [83]	≥140/90 mmHg or anti-HT	SLE	100	47	100	60	53
		Control	102	49	100		32.4
Sabio et al. [84]	≥140/90 mmHg or anti-HT	SLE	112	40	100	69	56.0
		Control	223	40	100		29.0
McMahon et al. [85]	≥140/90 mmHg or anti-HT	SLE	250	42	100	NR	77.0
		Control	122	41	100		20.0
Yang et al. [86]	≥140/90 mmHg or anti-HT	SLE	139	34	85	52	50.0
		Control	139	34	83		8.63
Bengtsson et al. [87]	≥140/90 mmHg	SLE	258	51	85	20[a]	36.8
		Control	516	48	85		24.4
Lertratanakul et al. [88]	≥140/90 mmHg or anti-HT	SLE	149	43	100	38	50.0
		Control	124	46	100		25.0
Barnardo et al. [89]	≥140/90 mmHg	SLE	178	41	88	NR	44.0
		Control	86	41	86		19.0
Rees et al. [89]	≥140/90 mmHg	SLE	7732	48	86	22	9.4
		Control	28,079	48	86	2	8.7
Medeiros et al. [90]	≥130/85 mmHg or anti-HT	SLE	146	42	92	NR	49.3
		Control	101	43	94		21.8
Tektonidou et al. [91]	> 139/89 mmHg or anti-HT	SLE	115	44	92	60	30.0
		Control	115	44			28.0

Anti-HT: antihypertensive therapy; GC: glucocorticoid use.
[a] ≥ 10 mg/day/intravenous pulse.
[b] Patients without increased intima media thickness.

2. Pathogenesis of hypertension in SLE

Hypertension is common in SLE but the underlying pathophysiologic mechanism is unclear. Although renal glomerular damage and renal vascular endothelial dysfunction are likely contributors, hypertension is also present in patients without renal involvement. Many possible mechanisms have been proposed to explain hypertension in SLE [5].

Lupus nephritis is present in almost 50% of SLE patients and has a well-established relationship with hypertension [6]. Despite the fact that hypertension may develop independently of lupus nephritis, not all histological lupus nephritis categories convey an elevated possibility of hypertension, with lupus nephritis class IV and V usually being related to hypertension [7], mainly because the glomerular filtration rate is decreased in lupus nephritis as a result of vasoconstriction. Renal tubular dysfunction probably also influences the pathogenesis of hypertension [8].

Lupus-related hypertension is believed to be part of the alteration of the vascular endothelial cell function [9], reflecting generalized endothelial dysfunction in SLE through the activation of endothelial cells [10]. Expanded circulating levels of endothelial progenitor cells and endothelial cells have been reported in SLE, which may demonstrate vascular injury [11]. Another possible mechanism is increased endothelin-1, which may provoke renal vasoconstriction and water and sodium retention [12]. The renin-angiotensin-aldosterone system (RAAS) and endothelin-1 both generate reactive oxygen species (ROS) and increase oxidative stress, which are crucial factors in the pathogenesis of both SLE and hypertension [13].

The RAAS regulates BP via the angiotensin-converting enzyme (ACE), which plays a relevant role in BP and blood volume homeostasis and provokes inflammatory tissue injury, usually through the angiotensin II receptor type 1. Studies have shown that RAAS is increased in SLE patients [14]. An insertion/deletion polymorphism in intro 16 of the ACE gene was reported to influence the development of hypertension, nephritis, and CVD in different ethnic populations [15]. However, no association was found between the ACE genotype or the allele and the development of hypertension in Asian SLE patients [16]. In a cross-sectional study, SLE patients had a significantly lower estimated 24-h urinary K^+ and higher estimated 24 h urinary Na^+: K^+ ratio than control subjects. It was also significantly associated with systolic and diastolic BP in SLE patients, underlining the potential role of Na^+ and K^+ intake on hypertension in patients with SLE [17,18].

Endogenous nervous system-immune interactions are known to control inflammation [19]. Dysautonomia has been associated with SLE, and these patients have decreased heart rate variability in the high frequency power domain, which indicates impaired efferent vagal tone [20]. A functioning efferent vagus nerve is thought to be necessary for proper neuroimmune communication in the cholinergic anti-inflammatory pathway, and since efferent vagal tone is decreased in SLE, perhaps this pathway in reducing inflammation is compromised.

SLE is a chronic, multisystemic, autoimmune inflammatory disease characterized by B and T lymphocyte hyperreactivity and the production of pathogenic autoantibodies leading to immune complex formation that are deposited in various tissues, including the kidneys, skin, joints, etc. Adaptive immune system dysfunction has been reported to be involved in the pathogenesis of hypertension in recent years [21]. Evidence suggests a role of abnormal B-cell activity in the pathogenesis of hypertension in certain populations and highlights the potential relationship between autoimmunity and hypertension [22]. Patients with active SLE without renal impairment had an increased frequency of high BP (43.4%) compared with patients with inactive SLE (25.7%) and controls (16.7%) [21]. Hypertension was associated with serologically-active disease and was influenced by increased T helper type 1 (Th1)/ Th2 linage cytokines, nitric oxide, insulin resistance and oxidative stress, without renal damage [22].

Recent studies support the role of dysregulated immune cell activity and chronic inflammation in the development and maintenance of hypertension. In general, elevated circulating pro-inflammatory cytokines, such as tumor necrosis alpha factor (TNF-α), interleukin (IL) -6 and B cell activating factor (BAAF), among others, are correlated with hypertension, indicating that peripheral inflammation may mechanistically contribute to chronic increases in BP [23]. Although the role of IL-6 (promoting B-cell hyperreactivity and increased production of autoantibodies) has not been examined in SLE hypertension, it correlates with essential hypertension [24]. Inflammatory cytokines interact with BP regulatory systems, such as RAAS [25] and the sympathetic nervous system [26]. TNF-α has also been shown to be elevated in SLE patients and may correlate with disease activity, but the role of TNF-α in SLE hypertension remains unclear [27]. Type I interferon IFN-α, which is increased in most patients with SLE, plays a crucial role in mediating endothelial dysfunction [28]. Whether or not elevated IFN-α influences renal hemodynamic function as a mechanism to develop hypertension in lupus remains unclear [29].

Among the effects of other inflammatory mediators, the induction of matrix metalloproteinases-2 and -9 (MMP-2 and MMP-9) and oxidative stress has been shown to be important in the development of SLE [28]. MMP-9 (C/T+ T/T) genotypes increase the risk of hypertension in SLE patients according to a cross-sectional study [30].

Autoantibodies that bind to and activate the major angiotensin receptor (AT1R) may contribute to disease pathophysiology and severity [31]. More recently, these autoantibodies have seen in patients with systemic sclerosis [32]. Angiotensin II type 1 receptor-activating antibody (AT1-AA) was closely associated with lupus nephritis in a cross-sectional study [33]. However, the impact of these autoantibodies in lupus-related hypertension has not been evaluated.

3. Anti-inflammatory therapy and hypertension

Besides lupus nephritis and systemic inflammation, the burden of hypertension in SLE patients may be increased by the use of some pharmaceutical agents. Polypharmacy is frequent in SLE patients [34]. Glucocorticoids and non-steroidal anti-inflammatory drugs (NSAIDs), which are used frequently in patients with various autoimmune diseases including lupus, occasionally contribute to resistant forms of hypertension [35]. A survey among rheumatologists showed treatment with NSAIDs was frequent in up to 84% of patients [36]. A systematic review of randomized controlled trials evaluating the effects on BP of NSAIDs, showed there was a significant increase in mean BP values in ibuprofen and indomethacin users compared with placebo [37]. However, low dose aspirin may not be associated with BP elevation [38].

Other immunomodulators, such as cyclosporine, may be linked to hypertension progression, although it is uncommonly administrated in SLE patients [39]. Fig. 1.

Many possible mechanism have been proposed to explain hypertension in SLE: lupic nephritis, glomerular and tubular dysfunction, hyperactivation of the Renin-Angiotensin-Aldosterone System (RASS), endothelin-1, endothelial dysfunction, and dysautonomia.

Other inflammatory mediators also have been implicated: IL-6, TNF-α (Tumor Necrosis Factor), IFN-α (Interferon), matrix metalloproteinases- 2 and 9 (MMP), and immune complex deposit tissues.

Some anti-inflammatory drugs also have relation with hypertension: glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs), and cyclosporine.

Hydroxychloroquine (HQC) has shown lower pulse wave velocity in premenopausal women, suggesting a potential protective effect against future major vascular disease [40]. Moreover, chronic HQC treatment reduced hypertension and endothelial dysfunction in severe lupus mice [41]. Early treatment with HQC prevents the development of endothelial dysfunction in a murine model of SLE [42].

Treatment with the immunosuppressive drug mycophenolate mofetil has been associated with a significant reduction in systolic, diastolic and mean BP in a small study in patients with rheumatoid arthritis and psoriasis. The effect of immunosuppression on hypertension in SLE patients has recently been studied in an experimental model of autoimmune disease. Female SLE and control (NZW/LacJ) mice were treated daily for 8 weeks with MMF. Mean arterial pressure was lower in SLE mice treated with MMF compared with vehicle-treated SLE mice. MMF also reduced both renal injury (urinary albumin excretion and glomerulosclerosis) and CD45R$^+$B cells and CD3$^+$CD4$^+$ T cells in kidneys from mice with SLE [43].

4. Impact of hypertension on outcomes

Atherosclerotic vascular events are more prevalent in SLE patients than in age-matched controls [1]. The exact contribution of each traditional vascular risk factor to CVD morbidity or mortality in SLE has not been completely assessed in prospective, randomized trials. However, some studies have shown that traditional vascular risk factors impact on the CVD burden in SLE [44–46]. Several studies have demonstrated that hypertension and/or the use of anti-hypertensive therapy were independently associated with the risk of cardiovascular events (Table 2) [47–50]. Ischemic stroke and stroke severity are not uncommon in SLE patients. Hypertension was found to predict a > 2-fold risk of stroke in SLE patients [51].

Beyond the influence of hypertension in CVD in SLE patients, it is an important predictor of damage accrual in these patients according to some studies [52].

Hypertension has also been associated with cognitive dysfunction, which is a common and debilitating manifestation in patients with SLE (OR: 2.06: 95% CI: 1.19–3.56) [53]. Fig. 2.

5. Diagnosis and definition of hypertension

The World Health Organization (WHO) reported hypertension and its effects on target organs (heart, kidneys, brain, etc.) to be the first cause of death worldwide. Therefore, hypertension evaluation and management should be the primary goal in all patients with SLE. Hypertension is more common in SLE patients than in the general population, with a prevalence ranging from 14% to 60% due to differences in the definition of hypertension used, the variability, reading-to-reading, of BP, and the methodologies used for measurement. Practices regarding cardiovascular risk assessment in SLE among rheumatologist have recently been determined using a questionnaire assessing preventive strategies, risk assessment and beliefs regarding SLE and CVD. Fifteen per cent of rheumatologists did not check the BP at every visit, 45% recommended a target BP of 140/90 mmHg and 55% recommended 130/80 mmHg. Cardiovascular risk assessment and preventive measures were inconsistent when rheumatologists monitored SLE patients [54]. BP measurements made in the physician's office is still the main way to diagnose hypertension; however, 24-h ambulatory BP monitoring (ABPM) has emerged as a valuable tool in determining BP because it provides a more accurate assessment with respect to office BP [55,56]. In addition to ruling out the white coat effect and masked hypertension, 24-h ABPM allows assessment of the circadian BP pattern, which been related to a greater or lesser cardiovascular risk [57].

Recently published guidelines such as the 2017 American College of Cardiology/American Heart Association (ACC/AHA) [58] and 2018 European Society of Cardiology/European Society of Hypertension guidelines [59] have substantial influence and contain slight differences worth examining. Despite their similarities, the guidelines take different positions in some areas. The most apparent is in classification of BP. The definition of hypertension in the European guidelines is unchanged, reflecting the level of BP (≥140/90 mmHg) at which drug treatment is recommended for all patients. In the recent iteration of the ACC/AHA guidelines [58], hypertension is defined by as mean systolic BP of at least 130 mmHg or diastolic BP of 80 mmHg or higher. This

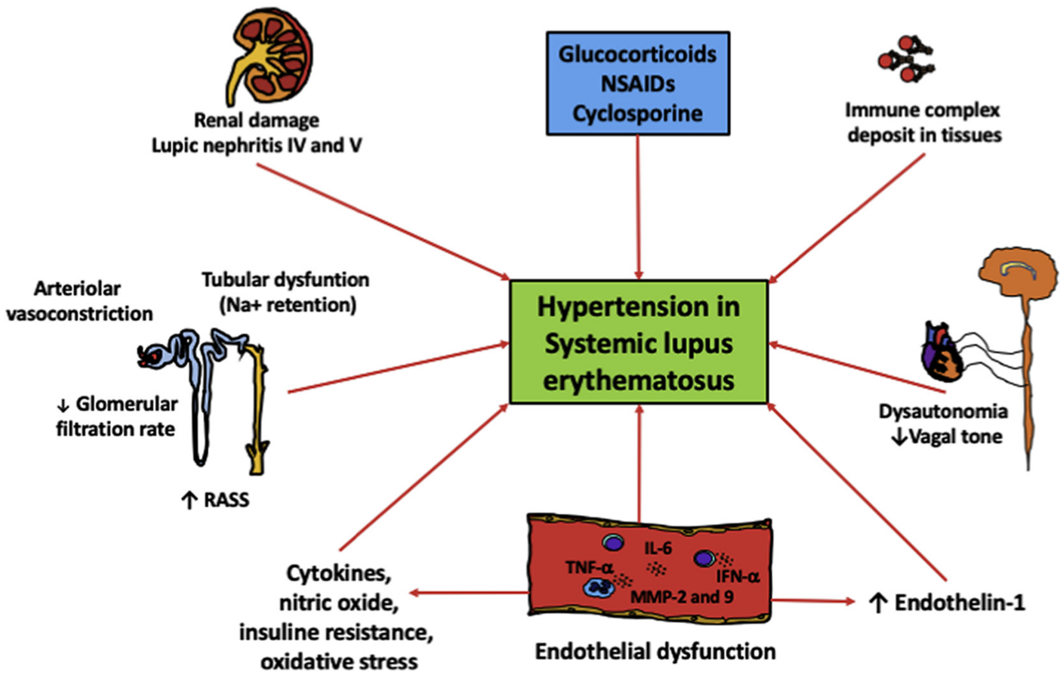

Fig. 1. Pathogenesis of hypertension in SLE.

results in a different approach to treatment adults with systolic BP of 130 through 139 mmHg or diastolic BP of 80 through 89 mmHg, who are classified as having stage 1 hypertension (Tables 3 and 4) [58,59].

6. Circadian blood pressure patterns and variability

There are several types of BP variability, depending on the time of assessment. In patients with rheumatic diseases, substantial changes in BP over time was reported in a large longitudinal cohort study of 1240 patients with SLE from the Toronto lupus cohort followed for a mean of 9.3 years [60]. In this study, SLE patients BP measurement varied between normal and elevated during the course of the disease, suggesting substantial variation in BP in SLE over time.

Lack of nocturnal BP fall (non-dipping) has been evaluated in SLE patients. BP physiologically declines by > 10% at night. Subjects who do not experience this drop are classified as non-dippers and are considered at higher risk of CVD [56].

Recently, 24-h ambulatory BP monitoring showed that SLE women were more likely to have an altered nighttime BP pattern than matched controls, and the non-dipper pattern and nocturnal hypertension were independently associated with increased subclinical atherosclerosis measured by carotid-femoral pulse wave velocity (PWV) [61].

Recently, a Spanish study evaluated possible relationships between vitamin D deficiency and the non-dipper pattern in SLE patients, using 24-h ambulatory BP monitoring: 62% were non-dippers and had lower levels of vitamin D than dippers [62].

In addition, 24-h ambulatory BP monitoring data has been analyzed in children diagnosed with SLE who presented with prehypertension or stage I hypertension without active lupus nephritis [63]. In this small study, nocturnal hypertension was detected in 60% and attenuated nocturnal BP dipping in 90% of both hypertensive and normotensive SLE patients.

Table 2
Review of studies of risk factors for heart disease in SLE patients.

Disease	Authors and year	Subjects	Age (years)	Design	Results
Coronary artery disease	Petri et al. [47]	229 patients	29–37	Longitudinal	OR: 3.5 (95% CI: 1.3–9.6)
Any CVE	Manzi et al. [1]	518 patients	34	Longitudinal	RR: 1.16 (95% CI: 0.52–2.57)
Any CVE	Toloza et al. [45]	546 multiethnic patients	36.5	Longitudinal	CVE vs. No CVE: 47.1% vs. 33.8%; No retained in the multivariable model
Any CVE	Bessant et al. [49]	29 patients	41–48	Longitudinal	Hypertension treatment associated with CVE (OR not showed)
Stroke	Mikdashi et al. [51]	238 patients	32.5	Longitudinal	OR: 2.3 (95%: 1.15–4.65) for any stroke OR: 3.17 (CI 95%: 1.38–7.32) for severe stroke
Carotid plaque	Zhang et al. [44]	111 premenopausal women	34.4	Cross-sectional	Plaque vs. No Plaque: 68.8% vs. 23.2% No multivariable analysis done
Any CVE	Urowitz et al. [3]	1249 patients from Toronto cohort	34.3	Longitudinal	CVE vs. No CVE: 73.6% vs. 32.3% No retained in the multivariable model
Any CVE	Bengtsson et al. [87]	269 patients	38.8	Longitudinal	HR: 2.90 (95% CI: 1.15–7.31)
Any CVE	Balloca et al. [92]	17,187 patients	39.5	Systematic Review	OR: 3.5 (95% CI: 1.65–7.54)
Any CVE	Fernández-Nebro et al. [93]	3649 patients from RELESSER registry	37.3	Cross-sectional	OR: 1.7 (95%: CI 1.20–2.44)
Valvular heart disease	Watad et al. [94]	5018 patients	50.2	Cross-sectional	OR: 1.69 (95%: 1.28–2.22)
Severe brady-arrhytmias	Tselios et al. [95]	52 patients	60	Cross-sectional	Permanent pacemaker (PPM) vs No PPM: 88.9% vs. 64.7

CVE: cardiovascular event; HR: Hazard ratio; RELESSER: Systemic Autoimmune Diseases Working Group of the Spanish Society of Rheumatology.

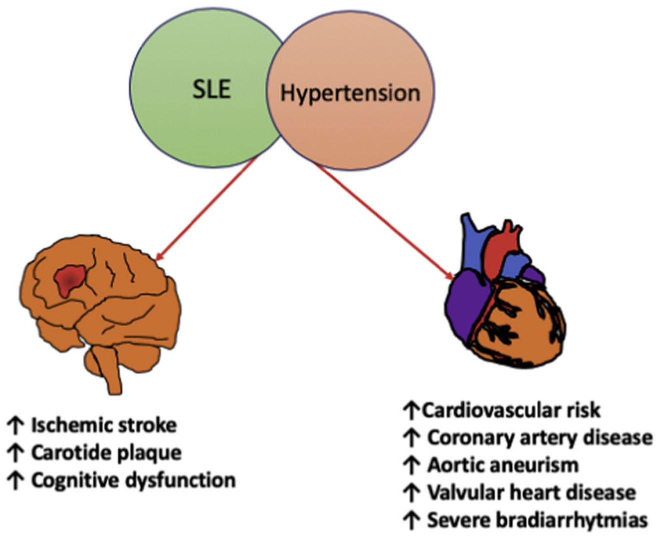

Fig. 2. Impact of Hypertension in Systemic lupus erythematosus.

Table 3
2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ ASH/ASPC/NMA/PCNA Guidelines for the prevention, detection, evaluation, and management of high blood pressure in adults. Categories of BP in Adults [58].

BP Category	SBP	DBP
Normal	< 120 mmHg	< 80 mmHg
Elevated	120–129 mmHg	< 80 mmHg
Hypertension		
Stage 1	130–139 mmHg	80–90 mmHg
Stage 2	≥140 mmHg	≥90 mmHg

DBP, diastolic blood pressure; and SBP, systolic blood pressure.

Table 4
2018 ESC/ESH Guidelines for the management of arterial hypertension. Classification of office blood pressure and definitions of hypertension grade [59].

Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	< 120	and	< 80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension	≥140	and	< 90

7. Management of hypertension in SLE patients

The primary objective of treatment is the maximum long-term reduction in the risk of cardiovascular morbidity and mortality. This requires the treatment of all associated vascular risk factors, including smoking, dyslipidemia or diabetes, and the correct management of hypertension-mediated organ damage, CVD and kidney disease, as well as the treatment of the BP rate per se.

Changes in lifestyle should always be recommended (reduction in salt and saturated fat intake, weight loss, smoking cessation, moderate alcohol intake, regular physical exercise).

7.1. Different therapies in experimental models with SLE

Early reports suggested that angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are more effective in controlling hypertension in SLE [64]. Although no randomized clinical studies have been performed thus far, experimental data in lupus-prone mice suggest that pharmaceutical RAAS inhibition reduces glomerular injury and proteinuria, along with transforming growth factor beta (TGFß) [65,66].

Recent studies have demonstrated the importance of cholinergic anti-inflammatory pathway regulation of pro-inflammatory mediators in chronic inflammatory disorders such as SLE [67]. Studies have investigated whether activation of cholinergic anti-inflammatory pathway at the level of the alpha 7 subunit of the nicotine acetylcholine receptor α7-nAChR) attenuates the development of hypertension in a genetic mouse model of SLE. Nicotine-treated SLE mice did not develop hypertension and this lower BP (compared with saline-treated SLE mice) coincided with lower splenic and renal cortical expression of pro-inflammatory cytokines [68].

N-acetyl-seryl-aspartyl-lysil-proline (Ac-SDKP) is a naturally-occurring tetrapeptide present in plasma, urine and several tissues including the heart and kidneys. It has been reported that Ac-SDKP exerts anti-inflammatory as well as immunoregulatory properties, and prevents hypertensive end-organ damage in addition to autoimmune myocardtitis and SLE [69]. Ac-SDKP prevented kidney damage, without affecting BP, in an SLE animal model. However, during the acute relapse of SLE, Ac-SDKP might also delay the manifestation of an acute and severe form of hypertension leading to early mortality [70].

Galantamine is a reversible acetylcholinesterase inhibitor that can cross the blood-brain barrier and act upon M1 muscarinic receptors centrally to potentiate efferent vagus nerve activity [71]. Recently, it was demonstrated that galantamine may be protective in SLE when administered chronically, attenuating splenic and renal inflammation, decreasing pathogenic autoantibodies and ultimately decreasing BP in a murine model of SLE [72].

7.2. Treatment guidelines and recommendations in SLE patients

Despite the existence of several hypertension therapeutic recommendations, this issue has not been addressed in SLE; therefore, it is unclear whether current guidelines can be implemented in these patients. In these circumstances, hypertensive patients with SLE with early disease and no overt renal and/or cardiovascular involvement are considered either with the general hypertensive population or without compelling indication for any specific antihypertensive drug [73].

The US guidelines recommend non-pharmacological therapy for all adults with stage 1 hypertension and additional antihypertensive drug therapy for the approximately 30% in this highly prevalent BP group who are deemed to be at high risk of CVD. In contrast, the European guidelines predominantly recommend lifestyle interventions, with consideration of antihypertensive agents only in adults at very high risk (i.e., with established CVD, especially coronary artery disease) (Table 5).

Other recent comprehensive BP clinical practice guidelines from Canada [74] and Australia [75] have also recommended lower BP treatment and agree that patients at high risk or very high risk (i.e., diabetes mellitus) should be treated if BP is 130/80 mmHg or higher with a treatment goal of < 130/80 mmHg.

SLE is an independent risk factor for the development of CVD, and is identified as such by the American Heart Association [76]. Therefore, antihypertensive drug therapy should be introduced if BP levels are 140/90 mmHg in patients without hypertensive-related organ involvement. In the case of renal involvement or diabetes mellitus, patients are considered at high or very high CVD risk and therapy should be implemented at lower levels (130/80 mmHg) [58,59,74]. The US guidelines recommends initiation of antihypertensive drug therapy with first-line agents such as thiazide diuretic, calcium channel blockers (CCBs) and ACE inhibitors or angiotensin receptor blockers (ARBs). Moreover, initiation of antihypertensive drug therapy with two first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended in adults with stage 2 hypertension (≥ 140/90 mmHg) and mean BP > 20/10 mmHg above their BP target; and

Table 5
2018 ESC/ESH Guidelines for the management of arterial hypertension. Ten year cardiovascular risk categories [58].

Very high risk	Documented CVD
	Clinical CVD: AMI, ACS, coronary or arterial revascularization, stroke, TIA, Aortic aneurysm, and PAD
	Unequivocal documented CVD on imaging: significant plaque (i.e. ≥ 50% stenosis) on angiography or ultrasound; it does not includes increase in carotid intima-media thickness
	Diabetes Mellitus with target organ damage: e.g. proteinuria or a with major risk factor such as grade 3 hypertension or hypercholesterolemia
	Severe CKD (eGFR < 30 mL/min/1.73 m2)
	A calculate 10 year SCORE of ≥10%
High risk	Marked elevation of a single risk factor, particularly cholesterol < 8 mmol/L
	Most other people with diabetes mellitus
	Hypertensive LVH
	Moderate CKD eGFR 30–59 mL/min/1.73 m2)
	A calculated year SCORE of 5–10%
Moderate risk	A calculated 10 Years SCORE of ≥1 to < 5%
	Grade 2 hypertension
	Many middle-age people belong to this category
Low risk	A calculated 10 year SCORE of < 1%

AMI = acute myocardial infarction, ACS = Acute coronary syndrome, BP = blood pressure; CKD = chronic kidney disease; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; LVH = left ventricular hypertrophy; TIA = transient ischaemic attack; PAD = peripheral artery disease; SCORE = Systematic Coronary Risk Evaluation.

initiation of antihypertensive drug therapy with a single antihypertensive drug is reasonable in adults with stage 1 hypertension and a BP goal < 130/80 mmHg with dosage titration and sequential addition of other agents to achieve the BP target. The European guidelines suggest that the five major drug classes (ACE inhibitors, ARBs, beta-blockers, CCBs and diuretics) should form the basis of antihypertensive therapy [59]. Some differences among these groups of drugs, based on a recent meta-analysis, have been reported (i.e., less stroke prevention with beta-blockers and less heart failure prevention with CCBs) [77].

Existing guidelines make no distinction between hypertensive SLE patients and the general hypertensive population with respect to follow-up during antihypertensive drug therapy and monitoring strategies to improve control of BP in patients on drug therapy for high BP. Once on antihypertensive drug therapy, all patients are recommended to return for monitoring and treatment adjustment at least every second month until they achieve their BP goal. Laboratory tests, particularly serum creatinine, potassium and microalbuminuria, should be monitored at least once or twice per year [58,59,74].

8. High blood pressure related to SLE-medications: general recommendations

As previously mentioned, the pharmacological treatment of SLE involves the use of some drugs that can increase or worsen BP levels, as well as interfering with antihypertensive drugs that, in many cases, are already part of treatment due to the high prevalence of essential hypertension in the general population. The main drugs are corticosteroids, immune suppressants and NSAIDs, which are used primarily in the control of articular symptoms.

In the treatment of corticoid-induced hypertension (mainly volume-dependent), discontinuation of corticosteroid therapy is recommended whenever possible. However, in cases in which treatment with corticosteroids can not be withdrawn, it is recommended to start treatment with a diuretic for the control of BP. Control of serum potassium levels is necessary, given the tendency to hypokalaemia that may be caused by corticoid-dependent hypertension and diuretic treatment [78].

In the treatment of hypertension induced or aggravated by NSAIDs, a calcium antagonist is recommended, and with relation of immunesuppressants the RAAS blockade should be considered as first line treatment when possible [78].

9. Conclusions

Traditional vascular risk factors, such as hypertension, increase the CVD risk in SLE patients. The pathogenesis and development of hypertension is likely to be multifactorial. Awareness of the risk of CVD and aggressive screening and treatment strategies, including meticulous BP control, have great benefits in high-risk populations such as diabetes patients. Awareness of the cardiovascular risk associated with SLE has increased, but is yet to be translated in a systematic approach aiming to reduce morbidity and mortality. Current clinical practice guidelines may not adequately apply to this particular group of patients. As direct evidence specifically in SLE is lacking, it seems reasonable to suggest that early detection and aggressive management of hypertension in patients with SLE should form part of such a systematic approach. There is a need for specifically-designed trials identifying approaches to hypertension management in patients with SLE, and quantifying the beneficial effect of hypertension control on the cardiovascular outcome of this group of patients.

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