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Review Article

Salt-Sensitive Hypertension in Aging: From Pathophysiology to Precision and Emerging Therapies

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ABSTRACT

Background: Salt-sensitive hypertension (SSHTN) is a multifactorial cardiovascular–renal disorder whose prevalence increases with aging. It contributes to cardiovascular disease, chronic kidney disease, frailty, and progressive target-organ injury. Beyond excessive sodium intake, SSHTN reflects systemic impairment of sodium homeostasis involving nephron loss, impaired pressure–natriuresis, endothelial dysfunction, arterial stiffening, immune dysregulation, mitochondrial impairment, and epigenetic remodeling.

Methods: This review summarizes and integrates current evidence on aging-associated SSHTN, focusing on epidemiology, biological mechanisms, multiorgan consequences, and emerging therapeutic strategies.

Results: Evidence indicates that aging links sodium excess to vascular and renal injury through several interconnected pathways, including non-osmotic tissue sodium accumulation, endothelial glycocalyx disruption, inflammaging, immunosenescence, cellular senescence, clonal hematopoiesis, gut microbiome remodeling, and mitochondrial dysfunction. Genetic and epigenetic alterations further contribute to impaired sodium handling, vascular dysfunction, and renal injury. These findings support the concept that SSHTN is a systems-level manifestation of biological aging rather than a purely renal disorder. Emerging therapeutic strategies include RNA therapeutics, senotherapeutic approaches, microbiome- and mitochondria-targeted interventions, regenerative cell-based therapies, and precision medicine frameworks.

Conclusion: Aging-associated SSHTN represents a multisystem disorder driven by impaired sodium handling and age-related biological changes across the kidney, vasculature, immune system, and metabolic networks. Available evidence underscores the need for mechanism-driven, biologically informed, and precision-guided strategies to improve prevention and treatment in older adults.

Introduction

Salt-sensitive hypertension as a phenotype of cardiovascular aging

Hypertension continues to be a major modifiable risk factor for cardiovascular morbidity and mortality worldwide. Despite advances in pharmacological therapy, blood pressure (BP) control remains suboptimal in a large proportion of patients, particularly in the elderly. Among hypertension subtypes, salt-sensitive hypertension (SSHTN) has been increasingly recognized as a clinically relevant phenotype characterized by exaggerated BP responses to dietary sodium intake (1, 2).

The pathological impact of dietary salt has been established over more than a century; however, recent

mechanistic evidence has shifted the conceptual framework from a purely hemodynamic disorder toward a multisystem disease involving renal, vascular, immune, and neurohumoral dysregulation. In this context, salt sensitivity is no longer considered a simple dietary response but rather a complex physiological trait reflecting systemic regulatory failure (1, 3).

A substantial body of experimental and clinical evidence identifies aging as a major determinant of salt sensitivity. Age-related changes in physiological mechanisms involved in sodium homeostasis contribute to increased salt sensitivity with aging, including decreased renal sodium excretion, increased arterial stiffness, endothelial dysfunction, and dysregulation of autonomic and hormonal signaling, which increase the likelihood that sodium loading will lead to persistent increases in arterial pressure (3, 4). Accumulating integrative evidence suggests that the geroscience framework offers a useful perspective for understanding the increased risk of SSHTN with aging. Several age-related processes have been linked to sodium-induced vascular injury including cellular senescence, mitochondrial dysfunction, epigenetic remodeling, and chronic low-grade inflammation. These mechanisms together reframe salt sensitivity from a primarily renal disorder to a systemic manifestation of biological aging (4, 5).

SSHTN as a multisystem disorder of biological aging

SSHTN is increasingly regarded as a multifactorial disorder that extends beyond the impairment of renal sodium excretion alone. Instead, it is a complex biological phenotype emerging from the interaction of renal, vascular, immune, metabolic, and neurohumoral pathways that together govern sodium homeostasis and cardiovascular adaptation to salt exposure (6, 7). Aging profoundly affects these regulatory networks. Progressive nephron loss, endothelial dysfunction, arterial stiffening, immune dysregulation, and mitochondrial impairment diminish physiological resilience to sodium loading. As a result, vulnerability to blood-pressure elevation and target-organ injury is heightened. Sodium not only has hemodynamic effects but also acts as a biologically active signal modulating inflammatory responses, endothelial function, oxidative stress, and tissue remodeling (6, 8).

Furthermore, recent studies have demonstrated that sodium can accumulate within tissues through partially non-osmotic mechanisms involving the skin, vascular wall, extracellular matrix, lymphatic system, and resident immune cells, challenging traditional volume-centered models of salt sensitivity. Instead, they support a broader framework in which maladaptive sodium biology contributes to cardiovascular–renal aging (9-11). Within this perspective, SSHTN may be viewed as a multisystem phenotype associated with biological aging, characterized by impaired sodium buffering, vascular vulnerability, chronic inflammation, and progressive organ dysfunction. Accordingly, this review integrates evidence from renal, vascular, immune, metabolic, genetic, and epigenetic studies, together with emerging therapeutic advances. The aim is to frame aging-associated SSHTN as a mechanism-driven geroscience phenotype and to highlight pathways that may support future precision-guided management.

Global epidemiology and clinical burden

Global burden of hypertension and sodium excess

Excess dietary sodium remains a major modifiable contributor to elevated BP worldwide. However, the cardiovascular impact of sodium exposure is not uniform, because individuals differ substantially in their blood-pressure response to salt intake (12, 13). This heterogeneity is clinically important because salt-sensitive individuals appear to experience greater cardiovascular and renal risk than salt-resistant individuals, even when baseline BP levels are similar. As populations age and sodium intake remains above recommended levels in many regions, aging-associated salt sensitivity is likely to become an increasingly relevant contributor to cardiovascular and renal disease burden (6, 14, 15).

Epidemiology and modifiers of salt sensitivity

Salt sensitivity of BP is estimated to affect approximately 25% of normotensive adults and nearly 50% of adults with hypertension, although estimates vary according to age, sex, ancestry, comorbidities, and the diagnostic protocol used to assess sodium responsiveness (14, 16). The phenotype is not limited to patients with established hypertension and may also occur in normotensive individuals, indicating broader biological variability in sodium handling. Aging, female sex after menopause, chronic kidney disease, obesity, diabetes, and ancestry-related genetic background have all been associated with greater salt responsiveness. These modifiers support the concept that salt sensitivity reflects impaired integration of renal, vascular, immune, metabolic, and neurohumoral regulation rather than dysfunction of a single pathway (7, 17, 18).

Aging as a central driver of salt-sensitive hypertension

Aging is one of the most powerful modulators of salt sensitivity, reflecting the cumulative structural and functional changes in the cardiovascular, renal, immune, and metabolic systems (1, 19). At the renal level, the age-related decrease in sodium excretory capacity contributes to impaired volume regulation. At the vascular level, progressive arterial stiffening reduces the buffering capacity against sodium-induced hemodynamic alterations. In addition, endothelial dysfunction and reduced nitric oxide bioavailability magnify vasoconstrictive responses to sodium intake (4, 8). Furthermore, mitochondrial dysfunction, epigenetic modifications, and chronic inflammatory activation have been identified as key contributors to age-related increases in salt sensitivity. Together, these mechanisms promote a pro-hypertensive phenotype characterized by enhanced vascular reactivity and impaired sodium homeostasis (5, 8).

Clinical and public health burden beyond blood pressure

The clinical implications of SSHTN extend beyond elevated arterial pressure. Salt-sensitive individuals are at increased risk of target organ damage, including renal dysfunction, vascular remodeling, and cardiac structural changes. Importantly, recent data suggest that sodium-related injury may occur independent of overt hypertension through direct effects on endothelial and immune pathways (2, 20).

From a public health perspective, population aging and persistent high dietary sodium intake represent a growing

global challenge. As life expectancy increases, the number of individuals at risk of salt-sensitive cardiovascular injury is expected to increase. This trend underscores the need for earlier identification of salt-sensitive phenotypes and preventative strategies that take into account biological aging, renal reserve, and cardiometabolic vulnerability (21, 22). The principal biological mechanisms linking aging to SSHTN, together with their major multiorgan consequences, are summarized in Figure 1.

Mechanisms of Salt-Sensitive Hypertension During Aging

Renal aging and dysregulated sodium homeostasis

Progressive nephron loss, glomerulosclerosis, tubular atrophy, interstitial fibrosis, and microvascular rarefaction all serve to diminish renal reserve and impair sodium excretion with age, resulting in a shift in the pressure–natriuresis relationship to one that favors sodium retention, thereby rendering BP increasingly dependent on higher arterial pressure to maintain sodium balance (15, 21). At the molecular level, distal tubular sodium handling is further altered by persistent WNK–SPAK–NCC activation, ENaC dysregulation, and the UMOD–NKCC2 axis. Inflammatory signaling, including TNF-α–dependent activation of the WNK cascade, has also been implicated in SSHTN in CKD (23-25). Parallel to this, age-related reductions in klotho signaling may promote oxidative stress, fibrosis, and increased renal vulnerability to hypertension-associated injury (26, 27). Because aging-associated SSHTN arises from coordinated alterations across renal, vascular, immune, metabolic, and sodium-buffering pathways, a systems-level overview of the principal mechanisms is provided in Table 1.

Table 1. Biological mechanisms underlying aging-associated salt-sensitive hypertension

System /Tissue	Key mechanisms	Aging-related alterations	Consequences for salt sensitivity and BP	Potential therapeutic targets	Ref
Kidney	WNK–SPAK–NCC signaling, ENaC activation, UMOD–NKCC2 axis, intrarenal RAAS dysregulation	Nephron loss, fibrosis, reduced renal blood flow, impaired pressure–natriuresis	Sodium retention, volume expansion, increased salt sensitivity	Thiazides, loop diuretics, MR antagonists, SGLT2 inhibitors, AGT-targeting RNA therapeutics	(15, 21, 23)
Vasculature	Endothelial dysfunction, glycocalyx injury, oxidative stress, arterial stiffening	Reduced NO bioavailability, endothelial senescence, extracellular matrix remodeling	Increased vascular resistance and sodium-induced pressor responses	RAAS inhibitors, MR antagonists, exercise, mitochondria-targeted therapies	(2, 28-30)
Immune system	Th17 polarization, NLRP3 inflammasome activation, SASP signaling	Inflammaging, immunosenescence, clonal hematopoiesis	Renal and vascular inflammation, impaired natriuresis	Anti-inflammatory strategies, senotherapeutics, NLRP3-targeted interventions	(31-34)
Mitochondria	ROS generation, impaired mitophagy, NAD+ depletion, reduced sirtuin activity	Mitochondrial dysfunction and metabolic aging	Endothelial injury, oxidative stress, vascular remodeling	NAD+ restoration, SIRT activation, mitochondria-targeted antioxidants	(4, 8, 15)
Gut–kidney–vascular axis	Dysbiosis, reduced SCFAs, increased TMAO and gut permeability	Reduced microbial diversity and barrier integrity	Immune activation, endothelial dysfunction, enhanced salt sensitivity	Dietary modification, probiotics, prebiotics, microbiome-directed therapies	(3, 32, 35, 36)
Tissue sodium buffering	Non-osmotic sodium storage, macrophage–VEGF-C signaling, lymphatic regulation	Glycocalyx degradation, impaired lymphatic clearance	Tissue sodium accumulation, vascular dysfunction, SSHTN	Sodium restriction, lymphatic-targeted and sodium-buffering strategies	(37-39)

Abbreviations: AGT, angiotensinogen; BP, blood pressure; CKD, chronic kidney disease; ENaC, epithelial sodium channel; MR, mineralocorticoid receptor; NAD+, nicotinamide adenine dinucleotide; NCC, sodium-chloride cotransporter; NKCC2, sodium-potassium-chloride cotransporter 2; NO, nitric oxide; RAAS, renin-angiotensin-aldosterone system; ROS, reactive oxygen species; SASP, senescence-associated secretory phenotype; SCFAs, short-chain fatty acids; SGLT2, sodium-glucose cotransporter 2; Th17, T-helper 17 cells; TNF-α, tumor necrosis factor-alpha; UMOD, uromodulin; VEGF-C, vascular endothelial growth factor-C; WNK, with-no-lysine kinase.

Vascular aging, endothelial senescence, and glycocalyx injury

Endothelial dysfunction, decreased nitric oxide bioavailability, oxidative stress, arterial stiffness, and endothelial senescence are the hallmarks of vascular aging. These alterations increase salt-dependent pressor responses and reduce vascular adaptation to sodium loading (2, 29). Endothelial glycocalyx damage has been found in recent mechanistic research to be a possible early predictor of salt sensitivity. High salt exposure can impair the glycocalyx's usual function of buffering sodium at the endothelium surface, increasing endothelial stiffness and facilitating sodium entry into vascular cells (24, 28). Vascular stiffness and hemodynamic amplification are also caused by extracellular matrix remodeling, collagen buildup, and elastin fragmentation (2, 23, 28). Glycocalyx breakdown is one of the first observable arterial anomalies that connects aging, sodium intake, and cardiovascular risk, according to imaging

and biomarker studies. Age-related salt sensitivity may further be exacerbated by the buildup of senescent endothelial cells and their SASP, which may further disrupt nitric oxide signaling, increase oxidative stress, and worsen vascular inflammation (40, 41).

Non-osmotic Tissue Sodium Storage and Impaired Sodium Buffering During Aging

Recent advances in sodium imaging and tissue biology have challenged the classic presumption that excess sodium is limited to the extracellular fluid compartment. Sodium can accumulate in the skin, skeletal muscle, vascular wall, and interstitial tissues via partially non-osmotic pathways mediated by glycosaminoglycan-rich extracellular matrices (42-44). These tissue sodium reservoirs seem to be under the control of macrophage- and lymphatic-dependent clearance pathways, and impairment of these buffering mechanisms may be a factor in endothelial dysfunction, vascular stiffening and salt-sensitive BP elevation (45-47).

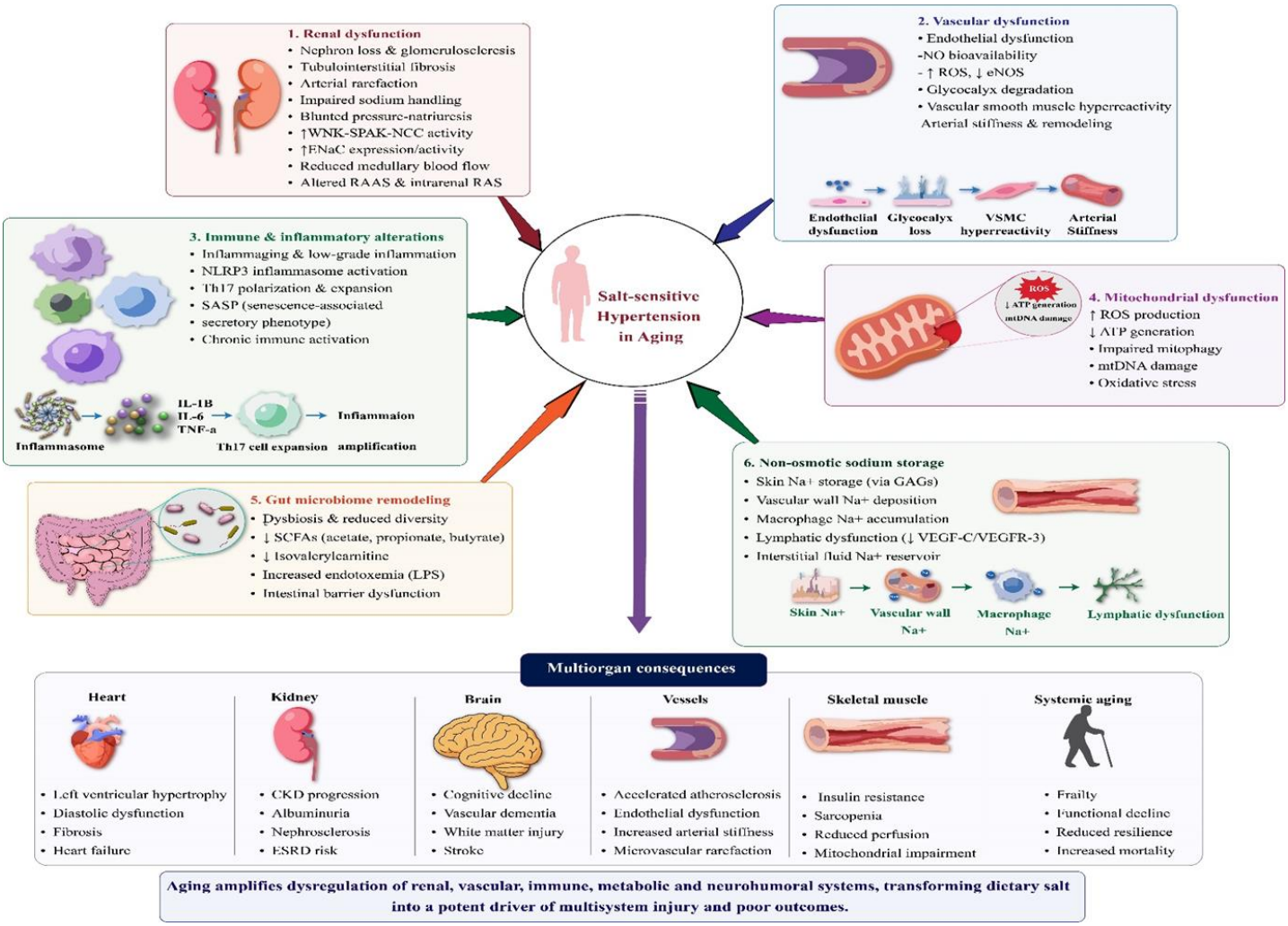

Fig 1. Systems-Level Mechanisms and Multiorgan Consequences of Aging-Associated Salt-Sensitive Hypertension. Aging promotes salt-sensitive hypertension (SSHTN) through coordinated dysfunction across renal, vascular, immune, metabolic, and sodium-buffering systems. Age-related nephron loss, impaired pressure–natriuresis, endothelial dysfunction, arterial stiffening, mitochondrial injury, chronic low-grade inflammation, gut microbiome remodeling, and non-osmotic tissue sodium accumulation synergistically disrupt sodium homeostasis and increase blood-pressure responsiveness to dietary salt. These interconnected mechanisms augment cardiovascular–renal vulnerability and promote progressive target-organ injury. Consequences extend beyond blood-pressure elevation to include cardiac remodeling, chronic kidney disease progression, cerebrovascular dysfunction, systemic vascular injury, metabolic impairment, sarcopenia, frailty, and accelerated biological aging. Together, these pathways support the concept that aging-associated SSHTN represents a multisystem geroscience phenotype and not an isolated disorder of renal sodium handling.

Aging may plausibly worsen this process through glycocalyx degradation, lymphatic dysfunction, chronic inflammation, and impaired tissue repair, although direct age-stratified human data are limited. Evidence from 23Na magnetic resonance imaging studies has demonstrated that tissue sodium accumulation can occur independently of overt extracellular volume expansion and may increase with aging(48-50). Experimental studies further indicate that macrophage-dependent activation of the VEGF-C–lymphatic pathway contributes to local sodium clearance, whereas dysfunction of this system promotes tissue sodium retention and vascular injury. These findings support the concept that tissue sodium buffering is an active biological process and may represent a previously underappreciated contributor to aging-associated SSHTN(15, 44, 46).

Inflammaging, immunosenescence, and immune reprogramming

These effects are amplified with aging due to the chronic low-grade inflammation and loss of immunological homeostasis. Exposure to salt promotes a pro-inflammatory immune phenotype with an increased IL-23-dependent pathogenicity, Th17 polarization through SGK1/NFAT5 signaling and increased production of TNF-α, IL-17A and other inflammatory mediators (16, 32, 33). These mechanisms promote renal salt retention, increase oxidative stress, and impair endothelial function. Salt intake is directly linked to innate immunological activation and SSHTN because high sodium also triggers ENaC-dependent inflammasome activation in antigen- presenting cells.

Aging worsens this response through immunosenescence, decreased Treg balance and the accumulation of senescent cells Producing SASP (16, 20, 24, 34).

Mitochondrial dysfunction and metabolic aging

Mitochondrial dysfunction has been identified as a major contributor to the amplification of SSHTN during aging. Exposure to high salt has been shown to cause mitochondrial structural and functional impairment, increased mitochondrial ROS production, decreased ATP synthesis, and disturbed oxidative phosphorylation in renal and vascular tissues (15, 21). Mitochondrial quality control is also reduced in aging tissues, and defects in mitophagy and mitochondrial dynamics may further accelerate oxidative injury.

Reduced Sirt3-mediated protection has been associated with endothelial dysfunction, vascular hypertrophy, vascular inflammation, and end-organ damage, supporting a direct mitochondrial contribution to the salt-sensitive phenotype. These changes support a feed-forward loop in which sodium excess exacerbates mitochondrial injury and mitochondrial injury further promotes SSHTN (15, 21).

Gut–kidney–vascular axis

Aging and high salt intake converge on gut dysbiosis, reduced microbial diversity, impaired barrier integrity, and altered immune signaling. Current evidence implicates the gut–kidney–vascular axis in SSHTN through effects on intestinal sodium handling, inflammation, and microbially derived metabolites (15, 51). In the multicenter MetaSalt trial, 528 participants underwent baseline, low-salt, and high-salt interventions; high salt altered 85 microbial species and 70 metabolites, and the gut microbiota-derived metabolite isovalerylcarnitine emerged as a signal inversely associated with salt sensitivity. In experimental models, higher isovalerylcarnitine attenuated SSHTN and improved endothelial function. These data support an emerging mechanistic role for the gut–kidney–vascular axis, but definitive causal translation in humans remains preliminary (36, 52).

Genetic and Epigenetic Architecture of Salt-Sensitive Hypertension During Aging

Genetic susceptibility and tubular signaling networks

Interindividual variability in salt sensitivity is strongly influenced by genetic susceptibility. Variants affecting RAAS signaling and distal tubular sodium transport have been linked to altered sodium handling, impaired pressure–natriuresis, and increased propensity to salt-sensitive blood-pressure responses. Representative genes include ACE, AGT, WNK1, WNK4, NEDD4L, UMOD, and SLC12A3. The effects of these variants are magnified in aging, as nephron depletion, tubular dysfunction, and reduced renal reserve progressively limit compensatory sodium excretion. As a consequence, genetic predisposition may translate into more pronounced pressure–natriuresis impairment and greater salt sensitivity in older individuals (53-56).

Epigenomic drift, chromatin remodeling, and biological aging

Aging-related epigenomic reorganization provides a mechanistic link between sodium exposure and sustained hypertensive phenotypes. Alterations in DNA methylation, histone remodeling, and non-coding RNA dysregulation have been associated with perturbed RAAS signaling, endothelial dysfunction, inflammation, and mitochondrial injury (19, 32, 57). Klotho downregulation is of particular relevance because decreased Klotho expression has been associated with endothelial stiffness, renal microvascular dysfunction, and rapid vascular aging. Persistent chromatin instability, defective DNA repair, and senescence-associated transcriptional reprogramming further reinforce pro-hypertensive signaling. These findings support the concept that biological aging may actively contribute to the development and progression of SSHTN rather than acting solely as a background modifier (19, 32, 58).

Non-coding RNAs and cellular senescence

MicroRNAs and long non-coding RNAs have been implicated in fibrosis, immune activation, endothelial dysfunction, oxidative stress, and extracellular matrix remodeling, suggesting a broader regulatory role for non-coding RNA networks in salt-sensitive cardiovascular and renal injury. In parallel, cellular senescence has emerged as a central upstream driver of salt-sensitive tissue damage. Senescent endothelial cells, tubular epithelial cells, vascular smooth muscle cells, fibroblasts, and immune cells accumulate with aging and release SASP mediators, including IL-1β, IL-6, TNF-α, MCP-1, TGF-β, and matrix metalloproteinases. These mediators promote chronic inflammation, fibrosis, vascular dysfunction, and sodium retention, thereby linking biological aging to progressive cardiovascular and renal injury in SSHTN (59-62).

Clonal hematopoiesis and aging-amplified inflammation

Recent experimental and translational studies implicate clonal hematopoiesis in age-related inflammatory remodeling and identify it as a potential modifier of salt-sensitive cardiovascular and renal injury (63, 64). In recent experimental work, TET2-associated clonal hematopoiesis was shown to predispose to renal hypertension through an inflammasome-mediated mechanism, and a related report indicated that Tet2-CH aggravated SSHTN in mice. These results suggest a potential role of age-dependent hematopoietic reprogramming in sodium-related vascular and renal injury, but a causative role for clonal hematopoiesis in the development of SSHTN in humans remains to be established (63, 65, 66). In this context, clonal hematopoiesis

should be considered along with inflammaging, immunosenescence, and endothelial senescence as elements of the broader geroscience architecture of SSHTN. Collectively, these genetic, epigenetic, and aging-associated regulatory mechanisms contribute to progressive dysfunction of multiple organ systems that ultimately shape the clinical manifestations and long-term consequences of SSHTN (32, 34). The integrated interactions of sodium accumulation, inflammasome activation, adaptive immune remodeling, inflammaging, cellular senescence, and clonal hematopoiesis in aging-associated SSHTN are summarized in Figure 2.

Multiorgan Damage Induced by Salt-Sensitive Hypertension

Cardiovascular injury

The combined effect of renal dysfunction, vascular aging, immune activation and metabolic remodeling ultimately translates into cardiovascular injury. Salt-sensitive individuals develop greater left ventricular remodeling, concentric hypertrophy, and myocardial fibrosis than salt-resistant hypertensive individuals (15, 67). Experimental and translational studies suggest that sodium excess promotes myocardial inflammation, fibroblast activation, extracellular matrix remodeling, and tissue sodium compartmentalization, suggesting that sodium acts as an active pathological substrate rather than a passive osmotic load (68, 69). Salt-sensitive aging is also associated with Heart Failure with Preserved Ejection Fraction (HFpEF)-like features, including diastolic dysfunction and ventricular–vascular uncoupling. Furthermore, atrial fibrosis and atrial fibrillation vulnerability have been demonstrated in salt-sensitive experimental models, supporting the concept that sodium excess can promote arrhythmogenic remodeling (70-72).

Renal injury

The kidney is a central mediator and primary target of SSHTN. Aging kidneys are increasingly susceptible to glomerular damage, progressive fibrosis, microvascular dysfunction, and decline of renal function as consequences of persistent salt-sensitive hemodynamic and inflammatory stress (19, 26). Sodium retention, endothelial injury, oxidative stress, and immune activation all contribute to progressive structural injury, including glomerulosclerosis and tubulointerstitial fibrosis. Proteinuria may be a marker of ongoing glomerular endothelial and glycocalyx injury and may further amplify tubular inflammation and fibrotic remodeling. Taken together, these processes position the kidney as a key player in target-organ damage in aging-associated SSHTN (2, 6, 73).

Cerebrovascular and neurocognitive injury

SSHTN is strongly associated with cerebral small vessel disease, impaired cerebrovascular reserve, and neurocognitive decline. Aging-related arterial stiffness transmits pulsatile energy to the cerebral microcirculation, promoting endothelial disruption, blood–brain barrier dysfunction, and microvascular rarefaction(2, 74). High sodium exposure has also been linked to impaired cerebral nitric oxide signaling, oxidative stress, and neurovascular uncoupling. Recent reviews support the view that dietary salt can impair vascular function and cognition, indicating that salt excess may damage the brain beyond its effect on systemic BP (75, 76).

Systemic vascular injury

Beyond their contribution to blood-pressure elevation, vascular abnormalities in SSHTN accelerate microvascular injury and amplify damage across multiple organ systems (77, 78). Endothelial dysfunction, glycocalyx disruption, arterial stiffening, and chronic vascular inflammation impair tissue perfusion and promote progressive target-organ damage. These alterations contribute to the development of albuminuria, cardiac remodeling, and cerebrovascular dysfunction, while simultaneously reducing the resilience of aging organs to hemodynamic and metabolic stress. As a result, vascular injury represents a central pathway linking sodium dysregulation to multiorgan complications in aging-associated SSHTN(79, 80).

Metabolic dysfunction, sarcopenia, and frailty

Further systemic burden of SSHTN arises from metabolic dysfunction. Insulin resistance and hyperinsulinemia may elevate activity of ENaC and NCC, and promote sodium retention, while endothelial dysfunction may impair perfusion of skeletal muscle and delivery of insulin(15, 21, 24). In older adults, frailty also modifies the clinical impact of hypertension and sodium restriction, highlighting that physiologic reserve plays a greater role in late life(81, 82). Over time, metabolic impairment, sarcopenia, and frailty may reinforce cardiovascular dysfunction and increase vulnerability to disability and hospitalization, supporting the interpretation of SSHTN as a systemic geroscience phenotype. The multisystem nature of organ injury in aging-associated SSHTN highlights the need for therapeutic strategies that extend beyond blood-pressure reduction and address the underlying biological mechanisms of disease progression(83-85).

Current Therapeutic Strategies in Aging-Associated Salt-Sensitive Hypertension

Current management of aging-associated SSHTN should be conceptualized as a volume–natriuresis–organ protection strategy rather than as generic blood-pressure lowering alone(8, 56). In contemporary guidance, sodium restriction remains foundational, while lower-sodium salt substitutes, usually potassium-enriched, may be considered with extreme caution in patients at risk of hyperkalemia, particularly those with impaired kidney function. From a mechanistic standpoint, sodium restriction reduces extracellular volume, attenuates vascular load, and decreases pressure-dependent renal sodium retention(86-88). In older adults, however, sodium control should be implemented in a way that avoids malnutrition and excessive dietary simplification. Dietary Approaches to Stop Hypertension (DASH)-style dietary therapy provides a practical nutritional framework for sustaining sodium reduction, because it improves potassium density, alkali load, and fiber intake while reducing exposure to ultra-processed foods(83, 89).

Potassium-enriched salt substitutes represent a promising nonpharmacologic strategy in older adults, particularly in phenotypes with high discretionary salt intake, but their use requires careful attention to renal function and hyperkalemia risk. The translational value of this approach is greatest in individuals whose sodium intake comes largely from cooking and table salt rather than from processed foods alone(88, 90).

When lifestyle measures are insufficient, pharmacotherapy should be aligned with the dominant pathobiology of salt retention. Thiazide and thiazide-like diuretics address distal sodium reabsorption, whereas loop diuretics become increasingly relevant as renal reserve declines. In older patients with nephron loss and vascular stiffness, sequential nephron blockade is often more effective than single-site blockade because the core problem is impaired natriuresis rather than isolated vasoconstriction(91-93).

RAAS blockade remains foundational, but high dietary sodium can blunt both the antihypertensive and antiproteinuric effects of ACEi/ARB therapy. Accordingly, RAAS inhibition should be viewed as part of the neurohormonal scaffold of treatment rather than a substitute for volume control. This is particularly relevant in aging-associated salt-sensitive disease, where the phenotype is often low-renin, volume-expanded, and fibrosis-prone(94-97). Mineralocorticoid receptor antagonism is a phenotype-concordant add-on in low-renin, salt-retentive disease. Evidence supports the blood-pressure-lowering efficacy of MR antagonists in low-renin hypertension, while finerenone has expanded the cardiorenal therapeutic armamentarium in CKD with diabetes and albuminuria, where anti-inflammatory and anti-fibrotic effects may matter as much as BP lowering itself (98-101).

SGLT2 inhibitors should not be framed as antihypertensive agents in the narrow sense. Rather, they are cardiorenal drugs with meaningful natriuretic and hemodynamic consequences, and recent CKD-oriented guidance has placed them within the nephroprotective backbone of care. In salt-sensitive phenotypes, their translational relevance lies in partially countering sodium-driven blood-pressure lability and preserving renal hemodynamic reserve(102-104). For refractory salt-retentive phenotypes, aprocitentan and renal denervation are emerging adjunctive options. Aprocitentan lowers ambulatory BP in resistant hypertension but may produce fluid retention, reinforcing the principle that vasodilation is unlikely to succeed if volume control is not optimized first. Renal denervation has regained clinical credibility through modern radiofrequency and ultrasound trials and may be considered an adjunctive option in carefully selected patients with resistant or uncontrolled hypertension(105-108).

Emerging and Regenerative Therapies

Current therapeutic approaches for SSHTN are directed towards blood-pressure control, sodium balance, and organ protection, but increasing insights into the biology of SSHTN have led to the development of mechanism-based, regenerative, and precision-oriented therapies that are directed at the underlying drivers of disease progression. The therapeutic landscape of SSHTN has shifted from empirical sodium restriction to mechanism-based interventions directed at specific biological pathways involved in sodium retention, vascular dysfunction, immune activation, and age-related cardiorenal injury(67, 109). Current strategies include RNA-based modulation of the renin-angiotensin system, device-based reduction of sympathetic overactivity, regenerative approaches directed at improving renal microvascular integrity, and experimental interventions directed at cellular senescence, microbiome remodeling, and mitochondrial homeostasis. Collectively, these approaches reflect a broader shift toward precision medicine frameworks that integrate biological phenotyping with individualized therapeutic selection(94, 110, 111).

Precision medicine and salt-sensitivity stratification

The first clinically relevant precision-medicine step in hypertension was the demonstration that polygenic risk scores improve the prediction of incident hypertension and cardiovascular risk. By 2022–2025, the field had moved toward multi-ethnic polygenic Risk Scores (PRSs), pathway-specific PRSs, and AI-optimized models integrated with imaging and clinical variables. For SSHTN, the key challenge extends beyond risk prediction to salt-response stratification. Similar levels of sodium exposure may produce markedly different phenotypes depending on renal reserve, vascular aging, and immune activation status (112-115).
Recent systems-biology studies have identified urinary proteomic signatures and kidney transcriptomic/proteomic signals associated with salt sensitivity of BP. Although these findings support the concept of biologically informed sodium management, their clinical utility remains investigational and requires prospective validation before routine implementation. In other words, the next precision step is to define who is truly salt responsive before escalating therapy(94, 116, 117).

Gene therapy and RNA therapeutics: from antisense proof-of-principle to clinically credible AGT silencing

The gene-therapy history of hypertension began with preclinical attempts to silence renin–angiotensin system genes. Early antisense, cDNA, and viral-transfer studies in rodent models established that AGT, ACE, AT1R, and related pathways could be modulated to lower BP, which was crucial because it identified AGT as an upstream and anatomically relevant target long before RNA therapeutics reached the clinic (118-120).

The first human translational step was IONIS-AGT-LRx, an antisense oligonucleotide targeting hepatic AGT mRNA. Phase 1 and phase 2 studies included healthy volunteers, individuals with mild hypertension after washout, and patients with uncontrolled hypertension on background therapy; across these studies, AGT levels fell, and blood-pressure trends were favorable, with no major on-target or off-target toxicity signal highlighted in the published summaries. Mechanistically, this established that hepatic AGT suppression is feasible in humans (121-123).

Zilebesiran further validated the therapeutic potential of hepatic angiotensinogen (AGT) silencing in hypertension (124). In the first-in-human study, 84 patients with hypertension completed treatment, demonstrating dose-dependent reduction in circulating AGT levels with sustained blood-pressure lowering after a single subcutaneous administration (125). The KARDIA-1 trial subsequently showed durable reductions in BP for up to six months in

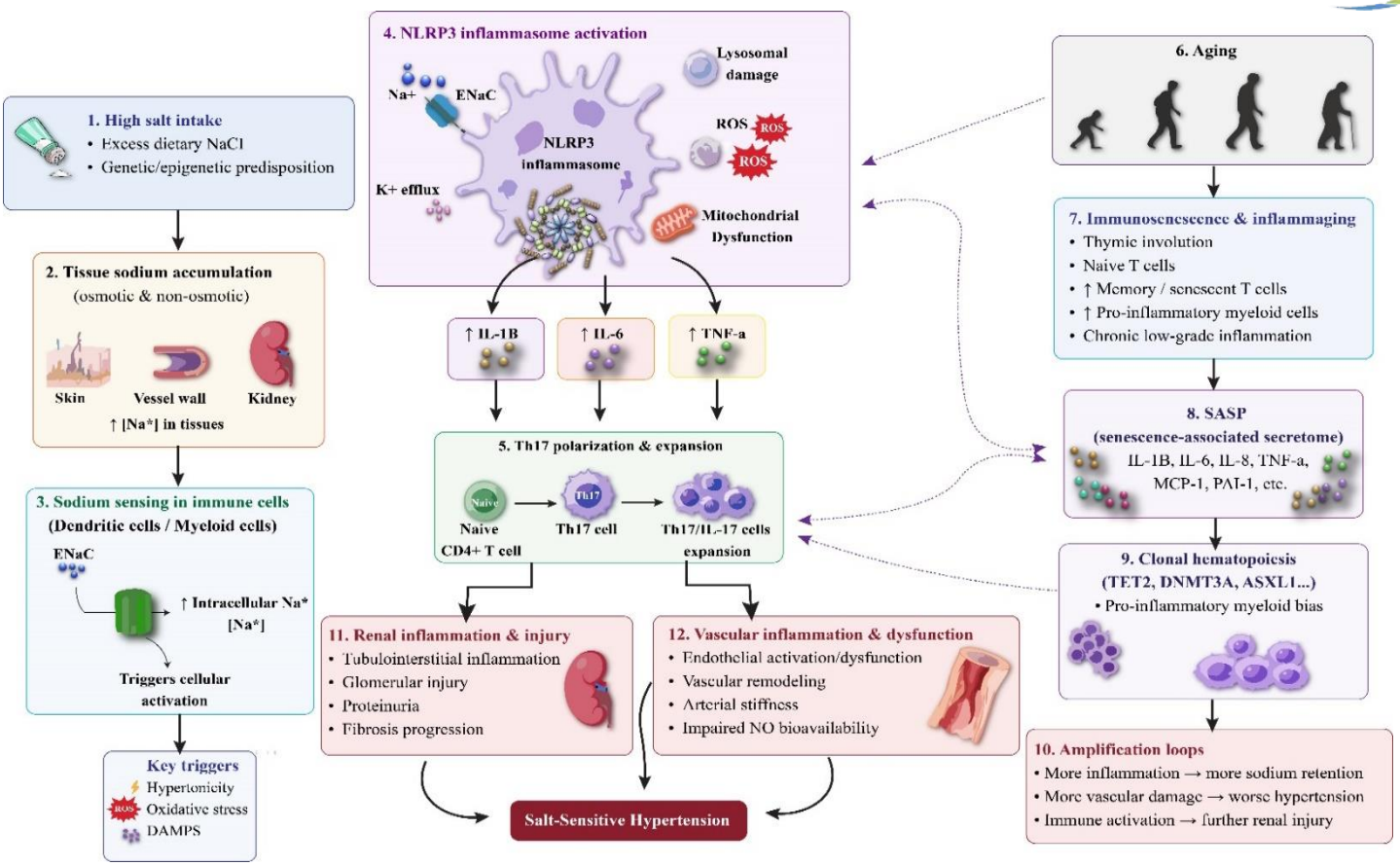

Fig 2. Immune, Inflammatory, and Senescence-Associated Mechanisms Linking Aging to Salt-Sensitive Hypertension. High dietary sodium favors tissue sodium accumulation and immune-cell sodium sensing, resulting in activation of the NLRP3 inflammasome and increased production of pro-inflammatory cytokines, such as IL-1β, IL-6, and TNF-α. These signals promote Th17 polarization and expansion, thereby amplifying vascular and renal inflammation. Aging further potentiates this process through immunosenescence, chronic low-grade inflammation (inflammaging), accumulation of senescent cells, and increased release of senescence-associated secretory phenotype (SASP) mediators. In parallel, clonal hematopoiesis may strengthen myeloid inflammatory bias and contribute to persistent immune activation. Together, these interconnected pathways establish self-amplifying inflammatory loops that promote endothelial dysfunction, arterial stiffness, renal injury, sodium retention, and progressive SSHTN.

patients with mild-to-moderate hypertension, while KARDIA-2 demonstrated that a single add-on dose reduced 24-hour ambulatory systolic BP by up to 12.1 mmHg at three months, with effects persisting through month six in selected cohorts. Together, these findings support the feasibility of long-acting RNA-based AGT suppression as a novel therapeutic strategy capable of providing sustained blood-pressure control with infrequent dosing (126, 127).

KARDIA-3 suggested that the antihypertensive response to AGT silencing may be attenuated in patients with advanced, treatment-resistant hypertension already receiving multiple background therapies. Although these results need to be confirmed in peer-reviewed publications and further studies, they suggest that therapeutic efficacy may differ depending on underlying disease phenotype and biological characteristics at baseline (124, 128-130). In parallel, tonlamarsen (ION904) has emerged as a second AGT-targeting RNA therapeutic platform.

Early clinical data demonstrated substantial suppression of circulating AGT levels together with favorable blood-pressure effects, although the relationship between target engagement and long-term clinical efficacy remains to be fully defined. Further studies are needed to understand how biomarker modulation translates into sustained therapeutic benefit (121, 131).

Genome editing for hypertension is still in the early preclinical stage. Experimental studies have shown that CRISPR–Cas9 mediated disruption of hepatic AGT can lead to sustained reduction in circulating AGT levels and BP in animal models. However, clinical translation has not yet been achieved, and substantial challenges in delivery efficiency, off-target editing, long-term durability, and safety continue to limit the application of genome-editing approaches in hypertension (119, 132).

Cell therapy and regenerative medicine: human evidence is narrow but biologically coherent

Cell-based therapies are promising regenerative strategies for a wide range of diseases, including cardiovascular disorders, chronic kidney disease, diabetes-related complications, and neurodegenerative diseases. The therapeutic effects of cell-based therapies extend beyond tissue replacement and include immunomodulation, angiogenesis stimulation, attenuation of fibrosis, and enhancement of endogenous repair mechanisms. These properties have generated increasing interest in applying cell-based therapies to hypertension and related cardiorenal disorders (133-140).

Cell therapy is a biologically plausible regenerative approach for SSHTN because it targets microvascular dysfunction, endothelial repair, inflammatory signaling, and tissue oxygenation rather than systemic hemodynamics alone. The strongest human evidence comes from the

renovascular disease program led by the Mayo group, which used autologous adipose-derived Mesenchymal Stem Cells (MSCs) delivered by renal-artery infusion into ischemic kidneys (141, 142).

In the 2017 first-in-man study, MSC therapy was associated with improved cortical perfusion and tissue oxygenation, while single-kidney function was stabilized relative to medical-therapy controls. This established the mechanistic logic of cell therapy in renovascular hypertension as microvascular rescue rather than hemodynamic rescue alone (143).

The 2020 phase 1a trial strengthened that signal. Across three dose tiers of 1.0, 2.5, and 5.0 × 10^5 cells/kg delivered by renal-artery infusion, renal blood flow increased, hypoxia and inflammatory biomarkers fell, mean systolic BP declined, and two-kidney GFR improved, with the largest effect in the high-dose group. This dose-response relationship is important as it suggests that MSC potency, not just cell number, is biologically relevant (143). Preclinical evidence is emerging that the antihypertensive effects of cell-based therapies may be more than simply microvascular repair and may involve immune and neuroimmune pathway modulation. However, underlying mechanisms are still poorly understood and warrant further investigation (144, 145). Table 2 summarizes major preclinical and clinical developments in regenerative and cell-based therapies for hypertension and SSHTN.

Senotherapy

Cellular senescence is increasingly recognized as a mechanistic amplifier of aging-associated SSHTN. Senescent endothelial, vascular smooth muscle, and renal cells contribute to endothelial dysfunction, arterial stiffening, and chronic inflammatory signaling through the SASP, while cardiovascular aging reviews link senescence to hypertension through oxidative stress, mitochondrial dysfunction, and persistent low-grade inflammation (8, 150, 151). Experimental senotherapeutic interventions have demonstrated the potential to reduce inflammation, improve vascular function, and attenuate age-related tissue injury in preclinical models. However, translation into clinical practice remains challenging. Recent geroscience reviews highlight that biomarker selection, tissue specificity, and trial-design challenges constrain clinical development, and current evidence does not yet support routine clinical use of senotherapy for aging-associated SSHTN. Therefore, senescence-targeted interventions should be considered promising but investigational approaches within the broader geroscience framework, as no clinical evidence currently supports their routine use in patients with aging-associated SSHTN (152, 153).

Microbiome-Directed Therapy

Growing evidence suggests that modulation of the gut microbiome may represent a novel therapeutic strategy for aging-associated SSHTN. Unlike mechanistic studies that establish the role of the gut–kidney–vascular axis in disease development, therapeutic approaches aim to restore microbial homeostasis and improve host–microbe interactions. Potential interventions include dietary modification, increased dietary fiber, prebiotics, probiotics, synbiotics, and metabolite-targeted strategies aimed at enhancing the production of beneficial microbial metabolites and reducing pro-inflammatory signaling (36, 52, 154). Experimental studies suggest that microbiome-directed interventions can improve endothelial function, attenuate systemic inflammation, and partially restore blood-pressure regulation in salt-sensitive states. Emerging metabolomic findings, including observations from the MetaSalt program, further support the possibility that microbiota-derived metabolites may serve as future therapeutic targets or biomarkers for treatment stratification. However, current evidence remains largely exploratory, and robust randomized clinical trials are still required before microbiome-based therapies can be incorporated into the routine management of SSHTN. At present, microbiome-directed therapy should be regarded as a promising but investigational component of precision cardiovascular medicine (36, 155, 156).

Mitochondrial Targeting

Mitochondria occupy a central position in cardiovascular aging because they integrate oxidative stress, inflammatory signaling, and energy failure. Recent reviews describe mitochondrial dysfunction as a major driver of aging and cardiovascular disease, and aging-related salt sensitivity has been specifically linked to mitochondrial dysfunction alongside epigenetic changes and altered gut microbiota. In vascular aging, mitochondrial dysfunction helps sustain a vicious cycle of oxidative stress and structural remodeling that can amplify salt-induced vascular injury (8, 157, 158). Therapeutically, mitochondrial autophagy enhancement, NAD+ modulation, and mitochondria-targeted compounds remain promising but early translational approaches. Contemporary reviews support the biological rationale for targeting mitochondrial dysfunction, yet they also underscore that definitive hypertension-outcome data are still lacking. Therefore, mitochondrial targeting should currently be framed as an investigational aging-directed strategy in SSHTN rather than an established therapeutic option (157, 159-161).

Device-Based Neuromodulation: Renal Denervation

Renal denervation has re-emerged as a credible adjunctive device-based option for uncontrolled and resistant hypertension. The 2024 American Heart Association scientific statement concluded that catheter-based renal denervation lowers BP versus sham in appropriately selected patients, and more recent evidence continues to support its use as an adjunctive rather than substitutive intervention (162-165). Within aging-associated SSHTN, renal denervation should be positioned as part of a phenotype-guided treatment algorithm rather than as a stand-alone solution. Its main relevance is in patients whose BP remains difficult to control despite optimized sodium reduction and pharmacotherapy, particularly when sympathetic overactivity contributes to residual risk (162, 166).

Future Directions and Precision Aging Framework

The next phase of SSHTN research is likely to move from blood-pressure-centric care toward precision modulation of the biological networks that govern sodium responsiveness and vascular aging. This will require integrated profiling of

genomic susceptibility, renal sodium-transporter biology, immune activation, endothelial senescence, mitochondrial function, gut-derived metabolites, and longitudinal digital cardiovascular phenotypes (6, 167-169).

Recent work in multimodal biomedical AI and cardiovascular precision medicine supports the feasibility of combining electronic health records, imaging, wearable signals, and multi-omics data to improve phenotyping, while hypertension-focused reviews highlight applications in risk prediction, remote monitoring, and digital therapeutics. In parallel, recent advances in wearable BP sensors and cuffless monitoring strengthen the case for high-resolution ambulatory phenotyping as a core input for future SSHTN endotyping (36, 88, 154, 170).

Translationally, the field is beginning to identify tractable intervention nodes. In the MetaSalt trial, a short-term salt intervention reshaped the gut microbiome and metabolome in 528 participants, and the microbiota-derived metabolite isovalerylcarnitine emerged as a signal linked to salt sensitivity and incident hypertension, reinforcing the rationale for gut–kidney–vascular targeting (36, 171). At the therapeutic level, KDIGO 2024 continues to support individualized RAS inhibition in albuminuric CKD, WHO guidance on lower-sodium salt substitutes underscores the need to balance sodium reduction with hyperkalemia risk, and the 2024 AHA scientific statement, together with modern trial data, has re-established renal denervation as an adjunctive option in carefully selected patients with uncontrolled BP (162, 172).

Taken together, these developments support a phenotype-based approach to future SSHTN research. Studies should focus on biologically distinct endotypes rather than heterogeneous hypertension cohorts. SSHTN should be viewed as a systems-level manifestation of cardiovascular–renal aging. Precision therapies are likely to be most effective when matched to the dominant biological driver in each patient (117, 173, 174).

Current Knowledge Gaps and Limitations

Despite extensive advances in understanding aging-associated SSHTN, many significant uncertainties remain. The causal contribution of non-osmotic tissue sodium accumulation, microbiome remodeling, cellular senescence, and clonal hematopoiesis in human SSHTN still needs to be established, and numerous of the innovative therapeutic approaches discussed in this review, including senotherapeutics, microbiome-directed therapies, RNA-based therapies, and regenerative cell-based strategies, are still supported mainly by preclinical or early-phase clinical evidence.

Table 2. Chronological Evolution of Cell-Based and Regenerative Therapeutic Approaches for Hypertension and Salt-Sensitive Hypertension

Year	Study	Cell Type / Therapeutic Platform	Model / Population	Route of Administration	Main Findings	Safety / Limitations	Follow-up	Ref
2014	Hu et al.	Mesenchymal stem cells (MSCs)	Dahl salt-sensitive rats	Renal medullary injection	Attenuated salt-induced hypertension and reduced renal inflammation	Preclinical study	20 days	(146)
2018	Otani et al.	Plasma-derived exosomes	SHR and WKY rats	Intraperitoneal administration	Improved vascular remodeling and BP regulation	Preclinical evidence only	6 weeks	(147)
2020	Abumoawad et al.	Autologous adipose-derived MSCs	Patients with renovascular hypertension	Intra-renal artery infusion	Improved renal blood flow, GFR, and BP control	Small sample size; early clinical experience	3 months	(141)
2021	Mayo Clinic group	MSC therapy	Atherosclerotic renovascular disease	Renal artery delivery	Improved renal oxygenation and microvascular function	Limited patient numbers	Variable	(148)
2024	Zhang et al.	hiPSC-derived MSCs	Spontaneously hypertensive rats	Intravenous administration	Reduced BP and modulated neuroimmune signaling pathways	Preclinical study	Several weeks	(144)
Emerging	Extracellular vesicle-based therapies	Cell-free regenerative therapy	Experimental models	Variable	Reduced oxidative stress and tissue injury	No robust human evidence	Experimental	(149)

Abbreviations: BP, blood pressure; GFR, glomerular filtration rate; hiPSC, human induced pluripotent stem cell; MSC, mesenchymal stem cell; SHR, spontaneously hypertensive rat; WKY, Wistar Kyoto rat.

Moreover, the biological heterogeneity of SSHTN and the absence of validated biomarkers for sodium responsiveness continue to hamper the application of precision-medicine approaches. Future longitudinal and mechanism-oriented studies will be essential to validate biologically distinct SSHTN endotypes and establish effective mechanism-based therapeutic strategies in aging populations.

Conclusion

Salt-sensitive hypertension (SSHTN) in aging is increasingly recognized as a complex multisystem disorder in which impaired renal sodium handling interacts with vascular aging, endothelial dysfunction, immune remodeling, mitochondrial injury, epigenetic alterations, and disrupted tissue sodium buffering; however, the relative contribution and causal importance of several emerging mechanisms remain incompletely established in humans. This integrated framework helps explain the marked heterogeneity in blood-pressure responses and target-organ damage observed among older individuals exposed to similar sodium loads. Future progress will require moving beyond uniform sodium-restriction strategies toward biologically informed identification of salt-sensitive phenotypes. Integration of renal, vascular, immune, metabolic, and tissue sodium biomarkers may facilitate more precise risk stratification and individualized management. Novel therapies, including RNA-based approaches, microbiome-directed interventions, senotherapeutics, mitochondrial-targeted strategies, regenerative cell-based therapies, and device-based neuromodulation, provide exciting opportunities to target underlying disease mechanisms rather than BP alone. Although many of these approaches are still investigational, ongoing advances in precision medicine and geroscience may ultimately facilitate mechanism-based prevention and treatment of aging-associated SSHTN.

Abbreviations

ACEi: Angiotensin-Converting Enzyme Inhibitor, **AGT**: Angiotensinogen, **ARB**: Angiotensin Receptor Blocker, **BP**: Blood Pressure, **CKD**: Chronic Kidney Disease, **CRISPR**: Clustered Regularly Interspaced Short Palindromic Repeats, **DASH**: Dietary Approaches to Stop Hypertension, **ENaC**: Epithelial Sodium Channel, **HFpEF**: Heart Failure with Preserved Ejection Fraction, **IL**: Interleukin, **iPSC**: Induced Pluripotent Stem Cell, **MCP-1**: Monocyte Chemoattractant Protein-1, **MRA**: Mineralocorticoid Receptor Antagonist, **MRI**: Magnetic Resonance Imaging, **MSC**: Mesenchymal Stem Cell, **NAD+**: Nicotinamide Adenine Dinucleotide, **NCC**: Sodium-Chloride Cotransporter, **NLRP3**: NOD-, LRR-, and Pyrin Domain–Containing Protein 3, **NKCC2**: Na^+–K^+–$2Cl^-$ Cotransporter 2, **NO**: Nitric Oxide, **PRS**: Polygenic Risk Score, **RAAS**: Renin–Angiotensin–Aldosterone System, **ROS**: Reactive Oxygen Species, **SASP**: Senescence-Associated Secretory Phenotype, **SCFA**: Short-Chain Fatty Acid, **SGLT2**: Sodium–Glucose Cotransporter 2, **SGK1**: Serum/Glucocorticoid-Regulated Kinase 1, **SIRT**: Sirtuin, **SSHTN**: Salt-Sensitive Hypertension, **TET2**: Tet Methylcytosine Dioxygenase 2, **TGF-β**: Transforming Growth Factor Beta, **Th17**: T Helper 17 Cell, **TMAO**: Trimethylamine N-Oxide, **TNF-α**: Tumor Necrosis Factor Alpha, **UMOD**: Uromodulin, **VEGF-C**: Vascular Endothelial Growth Factor-C, **WNK**: With-No-Lysine Kinase.

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