Hypertension Research (2024) 47:1246–1259
https://doi.org/10.1038/s41440-024-01642-6

REVIEW ARTICLE

Hypertension facilitates age-related diseases. ~ Is hypertension associated with a wide variety of diseases?~

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Received: 9 January 2024 / Revised: 21 February 2024 / Accepted: 22 February 2024 / Published online: 15 March 2024

Abstract

Hypertension, a disease whose prevalence increases with age, induces pathological conditions of ischemic vascular disorders such as cerebral infarction and myocardial infarction due to accelerated arteriosclerosis and circulatory insufficiency of small arteries and sometimes causes hemorrhagic conditions such as cerebral hemorrhage and ruptured aortic aneurysm. On the other hand, as it is said that aging starts with the blood vessels, impaired blood flow associated with vascular aging is the basis for the development of many pathological conditions, and ischemic changes in target organs associated with vascular disorders result in tissue dysfunction and degeneration, inducing organ hypofunction and dysfunction. Therefore, we hypothesized that hypertension is associated with all age-related vascular diseases, and attempted to review the relationship between hypertension and diseases for which a relationship has not been previously well reported. Following our review, we hope that a collaborative effort to unravel age-related diseases from the perspective of hypertension will be undertaken together with experts in various specialties regarding the relationship of hypertension to all pathological conditions.

Keywords Hypertension · Sensory organ damage · Urology · Dermatology · Orthopedics

Introduction

Hypertension is a major lifestyle-related disease and one of the age-related diseases. Hypertension induces vascular disorders such as accelerated arteriosclerosis and circulatory failure of small arteries, leading to ischemic organ damage such as cerebral or myocardial infarction, hemorrhagic organ damage such as cerebral hemorrhage and ruptured aortic aneurysm, and other fatal diseases, and is thus also known as a "silent killer". Hypertension is a primary disease and is the most significant risk factor for cerebrovascular and renal disease, and it is being addressed worldwide as a therapeutic target to overcome [1]. On the other hand, as advocated by Thomas Sydenham and William Oslar that "A man is as old as his arteries", impaired blood flow associated with vascular aging is the basis of pathogenesis in many organs. Such ischemic changes in target organs associated with vascular injury induce tissue dysfunction and degeneration, leading to organ dysfunction and aging. Since the vascular changes induced by hypertension are not limited to certain organs but extend throughout the body, hypertension is a risk factor for the inhibition of functional maintenance in all organs. Taking this background into consideration, we hypothesize that hypertension induces vasculitic ischemic changes in all organs and may be related to all age-related diseases, and attempt here to review the relationship between hypertension and diseases for which a relationship has not been much reported. It is undeniable that only a small portion of the diseases discussed here are related to hypertension, as many of them have been studied for a long time, and it is not possible to go into detail about the obvious relationship between hypertension and diseases or the detailed pathogenetic mechanisms. We here broadly and comprehensively present the relationship between hypertension and various diseases to show that hypertension has been reported to be associated with a variety of diseases. The main emphasis will be on the "hypertension causation

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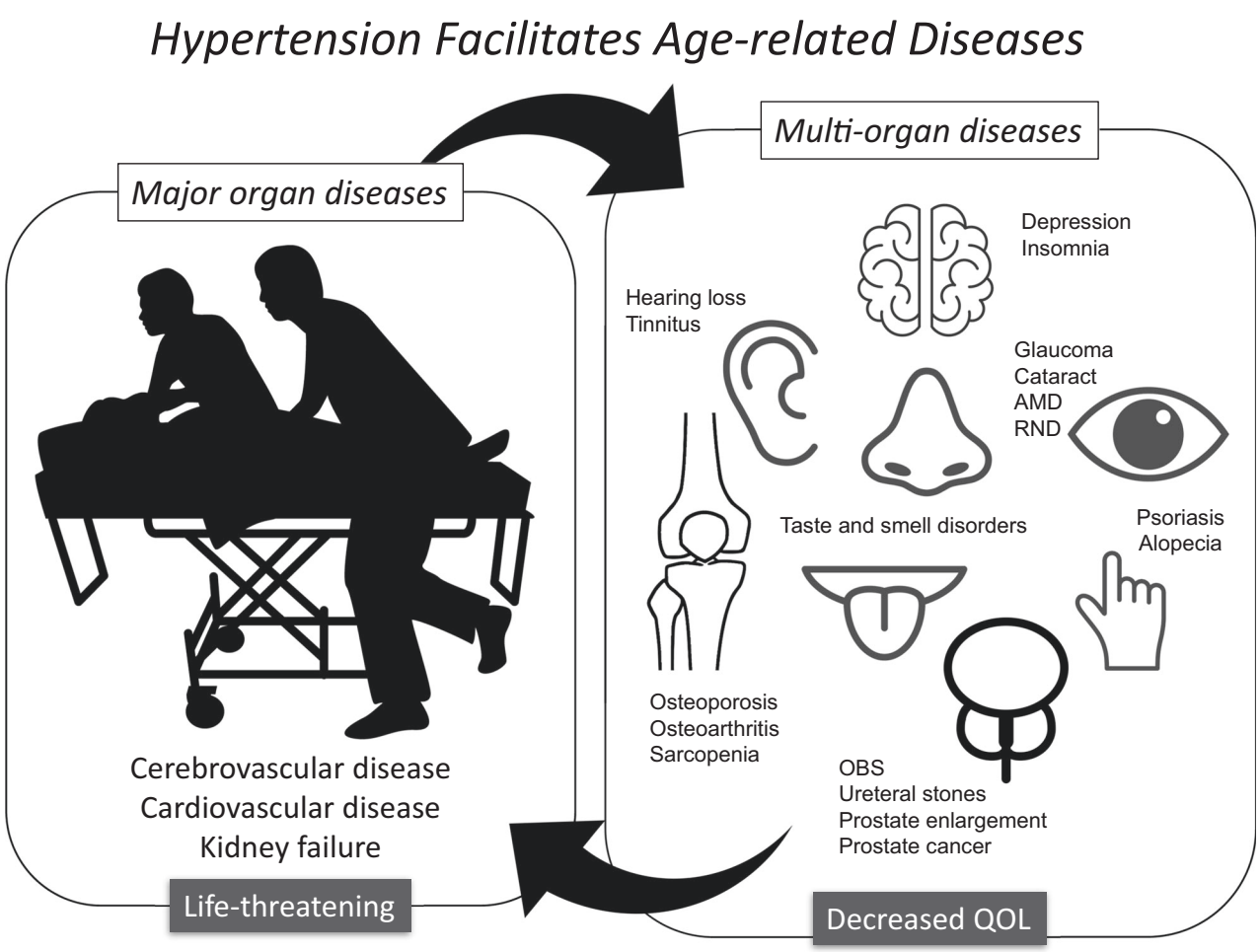
Graphical Abstract



theory", which states that hypertension induces various diseases. According to this perspective in mind, we hope to work with experts in various fields with expertise on hypertension, which affects all age-related diseases, to make joint efforts to clarify the relevance and pathophysiology, and to promote efforts to prevent and halt the progression of diseases through blood pressure management. We also hope to unravel age-related diseases from the perspective of hypertension, highlight the importance of measures against hypertension as a fundamental measure to prevent organ dysfunction due to aging, and promote joint efforts to extend healthy life expectancy.

Hypertension and sensory organ damage

Ophthalmology

In relation to the field of ophthalmology and hypertension treatment, fundus photography has long been used to detect hypertensive arterial changes, such as narrowing of arteries and irregularities in caliber, in advance of the development of symptoms and as an indicator of the systemic vascular status. Recently, more detailed imaging of retinal vessels is available, and it is known that such hypertensive retinopathy is a predictor of cardiovascular events [2]. Of course, hypertensive retinopathy also causes vision loss due to fundus hemorrhage and optic nerve edema. In addition, retinal arteriovenous occlusion and ischemic optic neuropathy are well known to be associated with hypertension, but relationships between other common ocular disorders and hypertension have also been reported. Here we mention the relationship between age-related diseases such as glaucoma, cataracts, etc., and hypertension.

Glaucoma

Although glaucoma is an optic neuropathy caused primarily by intraocular pressure, an association with blood pressure

has long been suggested, and a summarized review of glaucoma has been published in Hypertension [3]. To quote from the review: (1) Both high blood pressure (BP) and low BP are associated with an increased risk of glaucoma. (2) Low nighttime BP or excessive dipping could adversely affect glaucoma. (3) Systemic treatment with antihypertensive drugs has a minimal effect on intraocular pressure (IOP). Although there is no direct link between hypertension and glaucoma, there seems to be a link between glaucoma and blood pressure. BP variability particularly seems to play a role in the development of glaucoma. Thus, it is recommended that patients with hypertension should be screened for glaucoma, and conversely, that patients with glaucoma also should be screened for hypertension. Recently, a large cross-sectional study from Japan reported a significant association between higher systolic and diastolic blood pressure and raised IOP in the general population with no history of ocular disease, including glaucoma [4]. Leung et al. also reported a meta-analysis of the association between antihypertensive medication use and IOP: β-blocker use was associated with a lower odds ratio (OR) for developing glaucoma (OR = 0.83, 95% CI: 0.75–0.92), while the OR was higher with calcium channel blocker (CCB) use (OR = 1.13, 95% CI: 1.03, 1.24). No consistent associations were reported for other types of antihypertensive medications [5]. Also, in the Asian population, although the association was not strong, systemic use of β-blockers was associated with lower IOP, and systemic use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin (Ang) II type 1 (AT_1) receptor blockers (ARBs) was associated with higher IOP [6], but the relation to antihypertensive drugs is not clear. Very recently, Kastner et al. demonstrated an association between CCB use and glaucoma in a population-based cross-sectional study that included UK Biobank participants [7]. CCB users showed a 39% higher odds of glaucoma. Interestingly, because there was no relation between IOP and CCB use, CCB use may be involved in an IOP-independent mechanism of glaucomatous neurodegeneration.

It is known that the GCL and IPL thin in glaucoma. Huang et al. reported the effect of blood pressure on retinal neurodegeneration using a UK Biobank and a Chinese cohort study. Higher systolic and diastolic blood pressure, and most strongly higher mean arterial pressure, were associated with thinning of the macular ganglion intravitreal retinal lamina propria (GC-IPL) [8]. CCB use is reported to be associated with thinner GC-IPL and retinal nerve fiber layer (RNFL) thickness [7]. It has also been reported that in Asians, ACEI and diuretic use significantly promotes structural thinning of the RNFL and ganglion cell complex [9], and since chronic kidney disease is associated with capillary dilution [10], it has also been considered that because chronic kidney disease underlies the use of ACEIs, these renoprotective antihypertensive drugs are used and these retinal changes may also be influenced by chronic kidney disease and the causal relationship is unclear [11]. In a retrospective study, the association with antihypertensive drugs administered in patients with renal or cardiac disease would be inconclusive without interventional studies, as the possibility that elevated IOP may be induced in patients with disease cannot be ruled out.

The detailed mechanisms explaining the association between hypertension and glaucoma are not known, but it has been suggested that the renin-angiotensin system (RAS) is involved in the mechanism of elevated IOP [12]. For example, angiotensin II (Ang II) induces endothelial dysfunction of ocular arteries by promoting NADPH oxidase (NOX) 2-dependent reactive oxygen species (ROS) formation via type 1 receptors [13]. Glaucomatous optic neurodegeneration without progressive retinal ganglion cell loss and elevated IOP are reported in mouse ocular arteries after local or systemic aldosterone administration [14]. Loss of excitatory amino acid carrier 1 (EAAC1) is also believed to lead to retinal ganglion cell (RGC) degeneration without elevated IOP. Animal studies have shown that treatment with candesartan suppresses lipopolysaccharide (LPS)-induced inducible nitric oxide synthase (iNOS) production by inhibiting the TLR4-apoptosis signal-regulating kinase 1 (ASK1) pathway, and is effective in protecting retinal ganglion cells without affecting IOP [15]. In addition, in a rat model of induced hypertension, retinal function and blood flow were less affected by elevated IOP when exposed to chronic hypertension, even when acute blood pressure elevation was induced by intravenous injection of Ang II [16]. In addition, 4 weeks of chronic hypertension induced by subcutaneous injection of Ang II may result in structural changes in blood vessels caused by chronic hypertension, as the benefit of blood pressure elevation on retinal function in response to IOP elevation is impaired. Based on the results of these basic studies, the relationship between the RAS and glaucoma will continue to be investigated in depth, and the effects of antihypertensive drugs will be investigated in future clinical studies.

Cataract

The relationship between lifestyle-related diseases and the development of cataracts has long been investigated, and there have been numerous reports on the relationship between hypertension and cataracts. For example, Szmyd et al. reported in 1989 that hypertensive patients had an increased risk of cataract surgery with an OR of 1.49 (95% confidence interval [CI] = 1.06–2.09), and that the OR was even higher, 2.66 (95% CI = 1.66–4.23), when diabetes was present [17]. Interestingly, an increased risk of cataract

development was observed in hypertensive patients being treated with furosemide (OR = 1.95, 95% CI = 1.02–3.74). A 2008 cohort study of 35,369 Swedish women also reported that women with hypertension had a 12% increased risk of cataracts (rate ratio, 1.12; 95% CI, 0.99–1.26) [18]. A recent meta-analysis reported that hypertension is particularly associated with the risk of posterior subcapsular cataract (PSC) [19]. Previously, Bodakhe and colleagues reported that in cadmium chloride-induced hypertensive experimental animals, magnesium taurate prevented cataractogenesis via restoration of lenticular oxidative damage and ATPase function [20], and that the ARB olmesartan suppressed the development of cataracts in this model [21]. In response to these reports, a Korean group examined the relationship between antihypertensive medications and cataract, but the actual effect of hypertension and antihypertensive medications on cataracts is not clear, as the OR exceeded 1 in the diuretic, β-blocker, and CCB use groups, but only very slightly [22].

Regarding the mechanism, the hypertension and 2K1C models of Sprague-Dawley albino rats treated with 10% fructose and cadmium chloride ($CdCl_2$), respectively, showed significant cataract-inducing effects [23], but the changes were minor in the L-NAME-treated model. In addition, the degree of cataracts was reduced when ramipril was administered to the 2K1C model. The involvement of RAS has been investigated by the aforementioned group in a $CdCl_2$-induced Sprague-Dawley albino rat cataract model, and the mechanism is due to recovery of lenticular oxidative stress, ATPase function, and ionic contents in the eye lens [21]. They have reported similar findings elsewhere [24, 25], but thus far, no detailed molecular mechanisms have been elucidated.

Age-related macular degeneration

There are two main types of age-related macular degeneration (AMD): exudative (wet) type, which involves neovascularization of the choroid, and atrophic (dry) type, in which the retinal tissue atrophies. More than 20 years ago, Hyman et al. reported that exudative AMD was associated with moderate to severe hypertension based on an analysis of 1222 sets of photographs. They reported that exudative AMD was associated with moderate to severe hypertension [26]. Hogg et al. also reported an association between stage 2 hypertension and exudative AMD (OR, 3.21; 95% CI) [27]. On the other hand, a follow-up study of 3654 subjects in Australia could not identify an association between blood pressure and AMD [28]. Katsi et al. reviewed clinical studies [29], and reported that some reports showed an association with systolic blood pressure and pulse pressure, and others failed to show an association.

Basic research suggests that Ang II may be involved in dysregulation of the turnover of extracellular matrix (ECM) associated with loss of function of retinal pigment epithelial (RPE) cells, which is known to be an early stage in the pathology of AMD [30]. There are several types of matrix metalloproteinases (MMPs), and Ang II induces the activation of MMPs, leading to ECM dysregulation [31, 32]. However, we were unable to find any papers examining AMD in hypertensive mice.

Otolaryngology

In the field of otolaryngology, hearing loss has long been associated with hypertension. There are various causes of hearing loss, including congenital hearing loss, acute sudden hearing loss, chronic noise-induced hearing loss, and age-related hearing loss. Involvement of the RAS has also been reported for taste and olfactory dysfunction, suggesting an association with hypertension.

Hearing loss (age-related hearing loss and sudden hearing loss)

Although there have been reports for more than 50 years regarding the possible negative effects of hypertension on hearing loss [33], and although many studies conducted to date do not seem to have produced consistent results, hypertension is a possible risk factor for sensorineural hearing loss. For example, a recent paper in Hypertension Research reported an association between systolic blood pressure and hearing impairment in 13,187 Japanese subjects [34]. They found that higher systolic BP increased the risk of hearing impairment at 1000 Hz, but there was no clear correlation with BP in the 4000 Hz range. Reed et al. also reported that hypertension in middle age leads to hearing loss 25 years later [35]. Interestingly, Ting et al. speculated that persistent hypertension in middle to old age is associated with hearing loss and may be related to brain changes rather than inner ear changes [36]. Recent studies have also found an association between microvascular disease and hearing loss, as there is an increased risk of hearing loss when retinopathy is present [37]. Although the association with blood pressure was not examined in this paper, it has been suggested that microvascular damage induced by persistent hypertension is a risk factor for hearing loss.

On the other hand, sudden hearing loss may also be caused by a sudden interruption of the blood supply to the inner ear, for example, by infarction of the anterior inferior cerebellar artery (AICA) [38]. Therefore, the association between cardiovascular disease risk factors and sudden hearing loss has been the subject of numerous studies. In a recent examination of sudden hearing loss in patients with

vascular disease, Saba et al. reported a systematic review of 24 clinical studies of a total of 77,556 patients with sudden hearing loss [39], which showed that hypertension was a risk factor for sudden hearing loss (OR 1.5, 95% CI: 1.16–1.94). On the other hand, a systematic review of a total of 102,292 patients examined the association with lifestyle-related diseases such as hypertension in patients with sudden hearing loss, but pooled analysis of adjusted ORs showed no significant difference in risk with hypertension, and high levels of triglycerides (TG) and total cholesterol [40]. A report by Xie et al. also failed to show an association between sudden hearing loss and hypertension [41].

In basic research, McCormick et al. examined cochlear potential intensity in one-year-old spontaneously hypertensive rats (SHR) and Wistar Kyoto rats more than 40 years ago, and reported that the maximum potential intensity was lower in SHR [42]. This has led to the use of SHR as a model of age-related hearing loss, with papers showing that aging in SHR reduces inner ear hair cells but not the vasculature [43], the effect of ionic changes in cell potentials with hypertension [44], and that changes in Na,K-ATPase expression by inner ear sites in older SHR affect inner ear homeostasis [45]. It has also been suggested that SHR do not show an increase in inner ear blood flow when blood pressure is increased with Ang II, and that the autoregulatory capacity of blood pressure may be impaired [46, 47], suggesting vascular damage due to hypertension.

On the other hand, the development of an embolization model of the anterior inferior cerebellar artery (AICA) in rats [48], including the clinical studies described above, as a model for sudden hearing loss, suggests the influence of vascular damage on sudden hearing loss. However, we could not find any reports of sudden hearing loss in hypertensive models, since infarction is not easily induced in mice or rats by blood pressure effects alone.

Tinnitus

With regard to the possible association of tinnitus with hypertension, Figueiredo et al. reported a systematic review which tended to show an association in studies analyzing the incidence of hypertension in tinnitus patients, but not in studies evaluating the incidence of tinnitus in hypertensive patients [49]. On the other hand, Yang et al. also reported a possible association of hypertension with tinnitus with OR of 1.37 (95% CI: 1.16 to 1.62) based on a meta-analysis of 19 studies [50]. Reports from each region showed that although the numbers were small in South Africa with 106 hypertensive patients compared to 92 non-hypertensive patients, there was a significant difference, with tinnitus in 41.5% of hypertensive patients compared to 22.1% in the control group, A difference was also shown for tinnitus without hearing loss, in 17.7% versus 30.3% [51]. A longitudinal study of 900 patients in Brazil found a higher frequency of hearing loss and tinnitus in hypertensive patients, but the difference was not significant when adjusted for age [52]. In a recent report of 6198 subjects from the Canadian Health Measures Survey, ear health-related problems such as hearing loss and tinnitus showed an association with hypertension with an adjusted OR of 1.7 in men and 1.6 in women [53].

A possible mechanism suggested from basic research, although in an older paper, is that hypertension can impair the microcirculation in the inner ear and that antihypertensive drugs may have auditory toxicity [54, 55]. Since it has been reported that low systolic blood pressure and diuretic use are likely to induce tinnitus, as relates to antihypertensive drugs [56], it is speculated that this may be due to hypotension leading to microcirculatory and circulatory failure in the inner ear.

Disorders of taste and smell

For olfactory impairment, a 2-year follow-up study of 5190 Chinese subjects suggested a link between chemosensory function and blood pressure, as systolic blood pressure increased by 5.1 mmHg in those who developed changes in both taste and smell [57]. The impetus for this study was the fact that epithelial sodium channels (ENaC), which play an important role in fluid balance in the kidney, are also expressed in the taste buds of the tongue and are receptive to "saltiness". Experiments in mice have also shown that when Na flows into salt taste receptor cells via ENaC, action potentials are generated and neurotransmitters (ATP) are released through calcium homeostasis modulator (CALHM) 1/3 channels to the extracellular space and a salty taste is transmitted to the brain [58]. In addition, Sakamoto et al. showed that αENaC mRNA expression in the epithelium of the cardinal papillae was markedly reduced in mice with hypertension induced by aldosterone and NaCl. They showed that this may lead to decreased salt sensitivity and increased salt intake [59]. It has also been reported that the RAS components of renin, angiotensinogen, and angiotensin-converting enzyme are all present in the taste buds of fungiform and circumvallate papillae, along with ENaC, and that taste function is regulated by both local and circulating Ang II [60]. Interestingly, female mice born to mothers who were fed a high-fat diet from day 7 of gestation until lactation showed increased saltiness preference and increased AT_1 receptor expression in taste bud cells, indicating that saltiness preference is transmitted to the next generation via RAS [61]. These findings suggest a close relationship between hypertension and taste and olfactory disorders.

Hypertension and urology

Because salt intake and the kidneys play a major role in the development of hypertension, and because diuretics and RAS inhibitors are frequently used in antihypertensive treatment, there is a relationship between urologic symptoms and hypertension, especially those related to urinary drainage, but there are also numerous reports of relationships with prostate disease and other disorders.

Overactive bladder syndrome

A wide variety of relationships between urinary frequency and hypertension have been reported, including salt intake and salt sensitivity, increased renal blood flow in the supine position, parasympathetic nervous system effects, and antihypertensive medications such as diuretics. Therefore, we here focus on neurogenic bladder and overactive bladder syndrome (OAB). Pelvic hypoperfusion caused by salt intake atherosclerosis due to hypertension is a possible cause of lower urinary tract dysfunction, including OAB [62]. Therefore, hypertension, which is a factor in arterial stiffness, may be a factor in OAB, but there are few clinical studies. Very recently, Müderrisoglu et al. reported that in patients with both hypertension and diabetes, which are both risk factors for atherosclerosis, comorbidity of both conditions affected OAB symptoms and the treatment response [63]. On the other hand, the same group also examined the association with hypertension alone, but concluded that hypertension alone had little clinical relevance [64]. There are scattered studies using SHR in relation to the role of the autonomic nervous system in the mechanism of OAB [65]. In a study using SHR, the authors indicated that overexpression of RhoA may be involved in OAB associated with hypertension, and stated that bladder tissue-specific Rho-kinase isoforms could be found and selectively inhibited to reduce bladder overactivity without leading to excessive hypotension.

Kidney and ureteral stones

Although there have been reports of kidney and ureteral stones and hypertension being associated with each other as lifestyle habits, and on hypertension as a complication of ultrasonic disintegration, the prospective cohort study by Strohmaier et al. is probably the first to report that kidney stones themselves increase blood pressure [66]. They followed 252 patients with stones for 24 months and reported that systolic blood pressure decreased when stones were temporarily present and flushed out, but increased when stones were actively treated with extracorporeal shock wave lithotripsy (ESWL) or other modalities. Regardless of the type of treatment or location of the stones, both systolic and diastolic blood pressure were markedly higher after 24 months than before treatment. Chang et al. reported a higher incidence of kidney stones in patients with primary aldosteronism than in the general population [67]. It is hypothesized that the mechanism of this increase may be due to increased secretion of parathyroid hormone (PTH). The authors of the present review suspect that a decrease in urinary pH may be responsible for the formation of stones.

Prostate enlargement

Hypertension has long been reported to be associated with the pathogenesis of benign prostatic hyperplasia [68]. Steers et al. reported that early symptoms of an enlarged prostate-like state occur in young SHR [69], and since Golomb et al. showed that age-related prostatic hypertrophy develops in 1-year-old SHR [70], SHR have been used as a model of prostatic hypertrophy. Shimizu et al. reported that losartan administration suppressed the prostate enlargement observed in SHR [71]. SHR showed increased inflammatory cytokines and decreased blood flow in the ventral prostate and lower prostate, and increased prostate weight compared to WKY, but losartan treatment prevented these changes. In an older paper, losartan was also reported to prevent prostate enlargement by inducing apoptosis of prostate epithelium and increasing TGFβ1 expression [72].

Prostate cancer

Liang et al. reported that hypertension was associated with prostate cancer in a systematic review in 2016 [73]. They reported a risk of prostate cancer in hypertensive patients with RR 1.08 (95% CI 1.02–1.15). They discussed the possibility that sympathetic hyperactivity may lead to androgen-mediated stimulation of prostate cancer cell growth [74], the effects of abnormal aortic smooth muscle cell proliferation and lack of inhibitory system control seen in SHR [75], the inhibitory effects of RAS inhibitors on the presumed effect from the suppression of prostate cancer [76] and other factors, but the cause of the disease is not known. In a study by Navin et al. of 3200 prostate cancer patients in the U.S., a higher prevalence of hypertension was found compared to the general population [77], and the discussion suggested that both hypertension and prostate cancer may be mediated by androgen-based mechanisms. A recent article noted the development of hypertension with treatment using GnRH agonists [78].

Hypertension and dermatology

There have been numerous reports of skin diseases associated with the use of antihypertensive drugs [79]. On the other hand, the relationship between hypertension itself and skin diseases is discussed in the present article, which focuses on psoriasis and alopecia.

Psoriasis

Psoriasis is a chronic inflammatory skin disease and is also increasingly recognized as a systemic inflammatory disease associated with hypertension. Recent reports suggest that patients with severe psoriasis are at increased risk of hypertension, especially hypertension that is difficult to control. Abnormal activation of immune cells due to overexpression of pathogenic cytokines in psoriasis induces atherosclerosis, which further leads to hypertension [80]. Although it has been previously reported that psoriasis is associated with hypertensive complications [81, 82], the underlying inflammation-induced TNF-α and reactive oxygen signaling may be involved [83]. TNF-α induces differentiation transition of vascular smooth muscle from a contractile to a secretory form and promotes proliferation and production of extracellular matrix proteins associated with medial hypertrophy. It also affects the formation of neointima and atherosclerotic plaques by promoting lipid storage and enhanced motility of vascular smooth muscle cells. Such atherosclerosis may lead to increased vascular resistance to blood pressure. In addition, the TNF-α and interleukin (IL)-23/IL-17 pathways, which are increased in T cells such as Th17 and γδ T cells, are inflammatory pathways common to psoriasis and hypertension and are activated by angiotensin II [80]. Such systemic inflammation may be associated with elevated blood pressure.

Alopecia

Minoxidil was developed as an oral antihypertensive drug, but its side effect was hypertrichosis, and it is now used not as an antihypertensive drug but as a drug for alopecia. Minoxidil is a prodrug, and its active metabolite activates ATP-sensitive potassium channels, causing hyperpolarization of cell membranes and relaxation of vascular smooth muscle, resulting in hypotension. Triantafyllidi et al. reported that hypertensive patients with severe androgenic alopecia (AGA) have worse coronary microcirculation [84]. However, there do not appear to be any studies showing that the direct microcirculatory defects associated with hypertension are linked to hair loss. As for the relationship between mineralocorticoid receptors (MRs) and androgenic alopecia, Marie et al. have recently created mice that overexpress human MRs in the keratinocytes of the epidermis and hair follicles (HF). They reported epidermal atrophy, premature skin barrier formation, eye abnormalities, and alopecia [85]. Regarding the association between androgenic alopecia and hypertension, Ahouansou et al. reported an association with hypertension with an OR of 2.195 (95% CI: 1.1–4.3) in 250 white men aged 35–65 years [86], and there have been scattered reports of an association since then [87, 88]. However, we believe that it is debatable whether the excess of male hormones causes the increase in blood pressure, whether it is associated with increased aldosterone level, whether it is caused by hypertension or associated factors, and whether alopecia is caused by hypertension.

Hypertension and orthopedics

In the field of orthopedics, blood pressure elevation due to the use of analgesics is often experienced clinically, but in relation to pathological conditions, we here discuss osteoporosis, osteoarthritis, and sarcopenia.

Osteoporosis

The question of whether osteoporosis is increased in hypertensive patients can be traced back to 1968, when Kamiyama et al. reported that osteoporotic changes were greater in hypertensive women than in nonhypertensive women [89]. A study of the relationship between bone density and blood pressure in 3676 white women reported in the Lancet in 1999 [90] found that the rate of bone loss at the femoral neck increased with higher baseline blood pressure and was greater in the group with higher systolic blood pressure. In consideration, it has been suggested that in hypertensive patients, increased urinary calcium excretion relative to a given sodium intake and abnormal calcium metabolism due to hyperparathyroidism may be involved. On the other hand, Mussolino et al. recently reported in their analysis of the Third National Health and Nutrition Examination Survey (NHANES) that the relationship between hypertension and bone mineral density in postmenopausal women disappeared after correction for body mass index and other parameters [91]. Moreover, it is well known that osteoporosis is induced in Cushing's syndrome and pheochromocytoma. In Cushing's syndrome, secondary osteoporosis is induced by endogenous steroid overproduction, while in pheochromocytoma, the effect of increased sympathetic nerve activity due to increased catecholamines has been suggested. Elevated bone resorption markers have been reported in pheochromocytoma [92], and

resection of the adrenal gland improves osteoporosis [93]. The adrenergic signaling pathway and its neurotransmitters have been implicated in the development of post-menopausal osteoporosis [94]. In addition, sympathetic nerve activity has been implicated in bone resorption through receptor activators of nuclear factor-κB ligand (RANKL) expression via the β-adrenergic receptor on osteoblasts [95]. Thus, excessive sympathetic nerve activity may induce osteoporosis.

The relationship between osteoporosis and hypertension has been well studied in relation to the type of anti-hypertensive medication, and a review article was recently published [96]. ARBs, selective β-blockers, and thiazide diuretics have been shown to improve bone mineral density by stimulating osteoblast differentiation and reducing osteoclastogenesis, while nonselective β-blockers and dihydropyridine CCBs have no significant relationship with bone mineral density or bone strength, and α-adrenergic receptor blockers and loop diuretics appear to decrease bone mineral density and increase fracture risk. Although as mentioned above, the osteoporosis inhibitory effect of ARBs and selective beta-blockers may be due to the suppression of sympathetic nerve activity, regarding the relationship between the RAS and bone metabolism, Shimizu et al. reported that Ang II increases the expression of receptor activator of RANKL in osteoblasts and activates osteoclasts [97], which is supported by basic evidence. These results indicate that the association between Na diuresis and calcium excretion from the renal tubules associated with the development of hypertension and activation of RAS are related to bone metabolism, and that appropriate antihypertensive drug treatment for hypertensive patients may reduce the progression of osteoporosis and improve quality of life in female hypertensive patients.

Osteoarthritis

The most common comorbidity in patients with osteoarthritis (OA), hypertension, and the pathogenesis of OA have received much attention. In knee osteoarthritis, it has been reported that impaired blood flow in small vessels in subchondral bone at the edge of long bones may cause subchondral ischemia, which induces degenerative changes in cartilage and apoptosis of bone cells in the subchondral bone region, leading to OA progression [98]. A review by Ching et al. reported that hypertension can increase intraosseous pressure and cause hypoxia, which in turn induces remodeling of the subchondral bone and osteochondral junction. They also indicated that the effects of systemic activation of RAS and the endothelin system on the Wnt-β-catenin signaling pathway may regulate joint disease [99]. Funck-Brentano et al. also reported that low systolic BP is associated with high femoral neck BMD using data from the UK Biobank of 284,838 individuals [100]. In a basic experiment, Yeater et al. compared a model of osteoarthritis induced by medial meniscectomy in SHR and normotensive control rats, and found that female SHR mice with concomitant OA exhibited thinner cartilage and higher synovitis scores. Autonomic nervous system effects were suggested to be a factor in these findings [101]. Thus, the association between osteoarthritis and hypertension is a hot topic, as measures against locomotive syndrome are urgently needed in an aging society.

Sarcopenia

The relationship between the decrease in skeletal muscle mass and blood pressure can be discussed from various perspectives. First, regarding post-exercise blood pressure variation, some patients develop hypotension after exercise (post-exercise hypotension). In an interesting report, Cutler et al. reported that the synthesis of nitrite by oral bacteria affects blood vessels and promotes lower blood pressure and increased muscle oxygenation after exercise, based on a comparison of post-exercise gargling with antimicrobial gargles and placebo [102]. In addition, a recent collaborative study in mice by a number of Japanese researchers has shown that the moderate physical shock to the brain that occurs when the foot lands on the ground during moderate exercise moves the interstitial fluid in the brain and mechanically stimulates the cells of the blood pressure regulatory center in the brain, thereby decreasing the expression level of AT_1 receptors, which in turn decreases blood pressure. In humans, it was shown that sitting in a chair with an up-and-down seat surface may lower blood pressure by a similar mechanism [103]. The relationship between the RAS and sarcopenia was also examined in detail using genetically engineered mice by Yamamoto and Takeshita et al. who reported in particular the inhibitory effect of the ACE2/Ang 1-7/Mas axis on the protective arm of the RAS [104, 105]. Oh et al. found that Nox activity was increased in SHR, expression of hypoxia inducible factor (HIF)-1α, a marker of Th17 (RORγt), and IL-17 secreted by Th17 was increased in SHR, and a marker of Treg (Foxp3) and a cytokine secreted by Treg cells (IL-10) were decreased in SHR, possibly inducing sarcopenia [106]. As we have seen, SHRs have been used as animal models of various diseases, but whether hypertension is the basis of the pathogenesis, even though they exhibit hypertension, has rarely been investigated by simultaneously using anti-hypertensive drugs to lower blood pressure to the level in WKY, in a condition not related to blood pressure The true impact of blood pressure has not been investigated, and it is possible that chronic inflammation in SHR may enhance the

pathogenesis of the condition, and cooperation with hypertension specialists may be needed to determine the actual relationship between elevated blood pressure and the condition.

Hypertension and psychiatry

One subject in the field of psychiatry is the relationship between hypertension and dementia, which is not discussed here but is discussed in previous reports by the authors [107, 108]. In addition, dementia and psychiatric disorders associated with cerebrovascular disorders (cerebral hemorrhage, cerebral infarction, subarachnoid hemorrhage) associated with hypertension are omitted here. In this paper, we give an overview of depression.

Depression

Various reports have been published on hypertension and psychiatric disorders, and recently Schaare et al. reported an association between blood pressure and mental health based on data from over 500,000 people [109]. They found that higher systolic blood pressure was associated with fewer depressive symptoms, greater happiness, and lower emotion-related brain activity. Interestingly, impending hypertension was also associated with worse mental health many years before the diagnosis of hypertension. On the other hand, many studies have reported the prevalence of depression in hypertensive patients. A systematic review and meta-analysis by Li et al. found that the prevalence of depression in hypertensive patients was 26.8% (95% CI: 21.7% to 32.3%), or one in four [110]. This heterogeneity of reported results may be attributable to differences in assessment methods; the meta-analysis by Li et al. may be reliable because they included only studies that used interviews or pre-specified diagnostic criteria rather than self-reporting methods. Huangfu et al. also reported in the FinnGen Study of 42,857 cases and 162,837 controls that genetic susceptibility to depression increases the risk of hypertension, and stated the importance of blood pressure control in depressed patients [111]. Mrowitez et al. report an interesting review of why depression is more common in hypertensive patients. They considered that chronic inflammation in patients with psoriasis, an inflammatory skin disease, may also induce neuroinflammation, leading to depression and causing a high prevalence of depression as a complication in patients with psoriasis [112]. Although this hypothesis does not directly link hypertension to depression, if chronic inflammation associated with lifestyle-related diseases is accompanied by vascular and neuropathic damage, it may increase the likelihood that hypertension and depression coexist, if not cause them. In addition, the effects of lifestyle disruption and dietary deterioration associated with depression on hypertension should not be overlooked. In basic research, it is known that Ang II administration induces inflammation in the brain [113], and it is thought that Ang II, which does not cross the blood brain barrier (BBB), may cross the BBB and enter the brain in the presence of hypertension to induce brain inflammation [114] and may induce more cranial nerve disease. Further detailed studies are needed.

Insomnia

Resistant hypertension associated with sleep apnea syndrome (SAS) is well documented. For example, Peppard et al. reported in 2000 [115] that in the Wisconsin Sleep Cohort Study, the risk of developing hypertension after 4 years was 2.89 times higher in the group with a moderate apnea-hypopnea index (AHI) of 15 or higher, and 2.03 times higher in the group with a lower AHI of 5 to 15, indicating that sleep disorder is a risk factor for hypertension. The reason for this is thought to be that an arousal response occurs when breathing resumes after apnea, and a state of sympathetic hyperactivity occurs after a situation of parasympathetic dominance. Hypoxia and hypopnea also cause sympathetic hyperactivity [116]. Continuous positive airway pressure (CPAP) therapy decreases muscle sympathetic activity over time, resulting in a decrease in nocturnal and early morning blood pressure and the disappearance of blood pressure sleep surges [117]. It has also been reported that β-blockers are useful in lowering blood pressure in SAS patients with hypertension [118]. Thus, inhibition of good sleep leads to activation of the sympathetic nervous system, which is closely associated with increased blood pressure. On the other hand, orexin, a sleep-wake regulator, stimulates sympathetic preganglionics in rats [119], and increased activity of orexinergic neurons in the paraventricular hypothalamic nucleus has been reported in animal models of salt-sensitive hypertension [120]. The effects of orexin A on elevating inflammatory cytokines and increasing sympathetic innervation have also been reported in experiments using rats [121]. Since administration of an orexin receptor antagonist reduced blood pressure in SHR [122], it was expected that the orexin receptor antagonist, suvorexant, would show an effect in nocturnal hypertensive patients with insomnia (the SUPER-1 study). Unfortunately, however, no significant effect was demonstrated [123].

On the other hand, regarding whether hypertension induces insomnia, it is reported that the risk of insomnia is 1.5 to 3.18 times higher in hypertensive patients [124, 125]. There is some discussion that mental health problems such as anxiety and depression associated with hypertension may

be a factor, but the details of the relationship are not known. Although there are many links between hypertension and insomnia, it seems that hypertension is mostly recognized as one of the cardiovascular diseases induced by insomnia, and not as a factor inducing insomnia.

Others

Constipation

Constipation is also considered a risk for hypertension, and a recent Australian report of 541,172 hospitalized patients aged 60 years or older reported that constipation increases the risk of hypertension and cardiovascular disease in the elderly [126]. Constipation increases the risk of developing hypertension 1.96-fold (95% CI 1.94–1.99) and cardiovascular disease 1.58-fold (95% CI 1.55–1.61). Although the presence of hypertension alone increases the risk of cardiovascular disease 6.12-fold (95% CI 5.99–6.26), patients with both constipation and hypertension have a 6.53-fold increase in cardiovascular disease risk (95% CI 6.40–6.66). Kubozono et al. reported on bowel movements and blood pressure levels as well as blood pressure variability [127], but no daily bowel movement was found to be an independent factor leading to increased daily blood pressure variability over the year. In a commentary on this article, Mishima focused on autonomic influences on blood pressure variability and bowel motility, pointing out the importance of the gut-vascular axis, as autonomic dysfunction may be a common factor in blood pressure variability and constipation [128]. The relationship between intestinal bacteria and blood pressure will also be an important subject for future research, and if the intestinal bacteria that induce cardiovascular disease including hypertension have a microbiota that leads to constipation, then hypertension and constipation will be induced concomitantly. On the other hand, regarding whether hypertension induces constipation, the hypothesis of hypertension-induced constipation is unlikely because there are various triggers of constipation and no clear reports that microvascular disorders associated with hypertension induce constipation.

General geriatric syndrome

Various complaints and symptoms occur with aging and are referred to as geriatric syndromes, and frailty is one of them. Some geriatric syndromes are associated with hypertension itself, while others are associated with blood pressure variability. In addition, orthostatic hypotension and hypotension induced by antihypertensive medications can be triggers, and there is a wide range of factors related to the interaction of many medications - polypharmacy. In the SONIC study, Kabayama et al. reported a negative correlation between systolic blood pressure and geriatric syndrome [129]. In the elderly, low blood pressure may play a role in geriatric syndromes, and careful antihypertensive treatment may be required. On the other hand, heart failure is associated with various complaints, and a meta-analysis

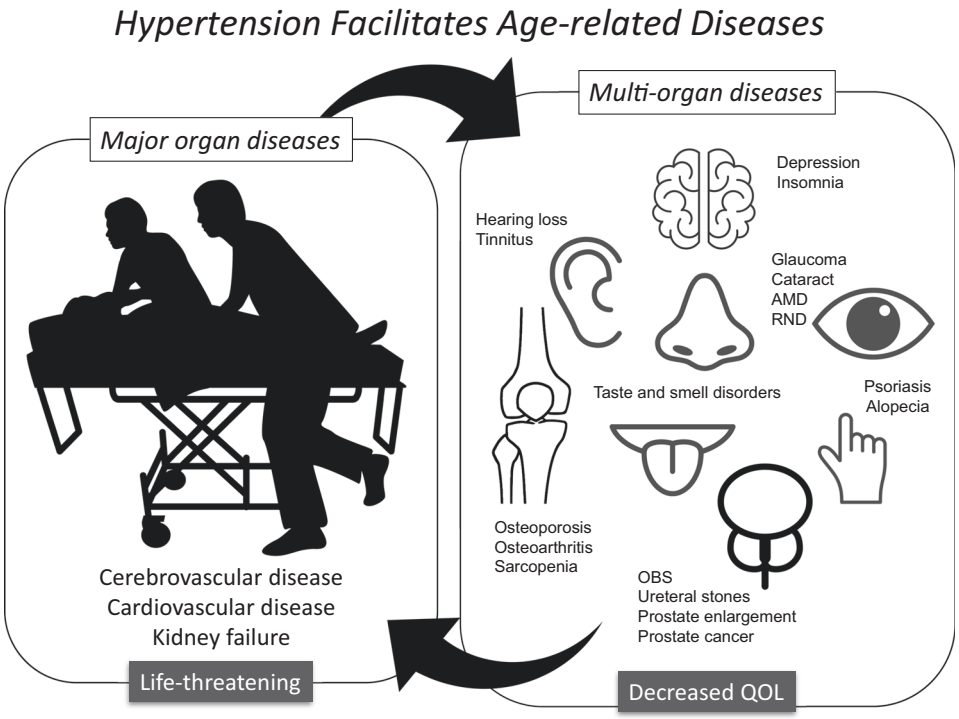


Fig. 1 Systemic diseases reported to have a possible causal relation with hypertension in this review. AMD age-related macular degeneration, RND retinal neurodegenerative diseases, OBS overactive bladder syndrome

reported that more than 40% of heart failure patients are found to have frailty [130]. When geriatric syndrome is suspected, it is important to exclude systemic diseases such as heart failure, and since hypertension is a major factor in heart failure, antihypertensive treatment to prevent heart failure should be considered. Thus, antihypertensive treatment to prevent heart failure is an important approach to prevent geriatric syndrome in the elderly.

Conclusion

This paper presents an overview of the relationship between hypertension and disease, focusing on diseases that have been less commonly associated with hypertension. Hypertension is the most important risk factor for cardiovascular disease, but it is also a disease of aging. It is associated with not only aortic atherosclerosis but also microcirculatory disturbance and may induce impaired blood flow in various organs. Although it will be necessary to conduct studies, including basic research, on the relationship between hypertension and aging-related diseases, such as whether hypertension is the cause, whether the condition induces hypertension, or whether the two diseases are completely independent and only coexist because they are age-related diseases, the impact of hypertension, which affects a very large number of patients, on age-related diseases is probably greater than we can imagine, and we look forward to future research in many fields beyond those of hypertension researchers (Fig. 1).

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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