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REVIEW

Hypertension as a Major Risk Factor in Alzheimer's Disease: Mechanisms, Interactions and Therapeutic Perspectives

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Abstract: Alzheimer's disease (AD) and hypertension (HTN) are closely related pathophysiological pathways that have a major impact on cognitive impairment in later life. Chronic high blood pressure exacerbates neurodegenerative processes by accelerating cerebrovascular dysfunction, impairing the clearance of amyloid-β (Aβ), promoting tau pathology and causing microvascular damage. Through mechanisms such as endothelial dysfunction, blood-brain barrier (BBB) disruption, white matter hyperintensities, cerebral microbleeds, and decreased cerebral perfusion, midlife HTN is consistently a strong predictor of late-life dementia. Neuropathological and biomarker analyses demonstrate that HTN is strongly linked to tau burden, neuronal death, and regional brain atrophy, even in the presence of continuous amyloid deposition. Experimental evidence showing that HTN enhances Aβ deposition, neuroinflammation, and small vessel disease, all of which contribute to cognitive decline, thereby supporting the vascular theory of AD. Antihypertensive medications, particularly those that target the renin-angiotensin system, have promising neuroprotective benefits and somewhat lower the prevalence of dementia. This review suggests that controlling blood pressure throughout life could significantly reduce the global incidence of dementia. In addition to being a major vascular risk factor, HTN also acts as a separate accelerator of neurodegeneration linked to AD. This highlights the need for early detection and continuous blood pressure medication as practical, scalable preventive measures.

Keywords: hypertension, Alzheimer's disease, neuropathology, clinical biomarkers

Introduction

Chronically high blood pressure (HBP) or hypertension (HTN) is one of the most important modifiable risk factors associated with Alzheimer's disease (AD). An estimated 1.3 billion people worldwide suffer from HTN, which is the primary cause of strokes and cerebrovascular illness.[1] The risk of vascular dementia (VaD) is positively correlated with midlife HTN but not with late-life HTN.[2] Antihypertensive medication is linked to a more modest decrease in dementia risk; recent meta-analyses of clinical trials have reported a 7–11% relative risk reduction. Whereas midlife-HTN has been demonstrated to increase the relative risk of lifetime dementia by roughly 20–54%.[3] AD specific meta-analyses have shown conflicting results; some have found no significant association between mid-life or late-life HTN and AD, while others have suggested that mid-life HTN may increase the risk of AD by 18–25%.[4] However, considering the high lifetime incidence of both dementia and HTN, even such small relative risk reductions brought about by antihypertensive medication use constitute a significant drop in the absolute global prevalence of dementia.[5] High blood pressure induced oxidative stress and vascular dysfunction also harm brain health and hasten dementia. In the most recent meta-analysis to date, Ou et al 6 found that. In contrast, late-life HTN (>65 years) was not significantly associated with AD; mid-life HTN was associated with a 19% higher risk of late-life AD.

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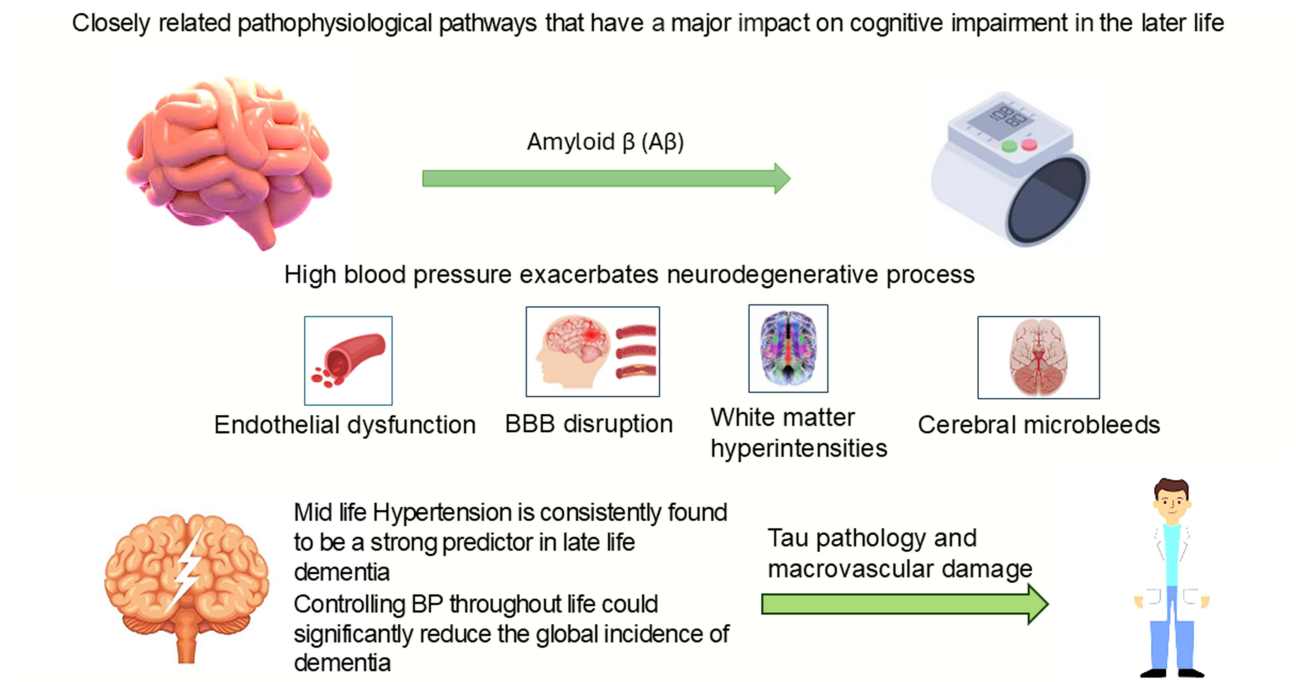
Graphical Abstract



Recent detailed reviews have also acknowledged HTN as a potentially changeable factor that influences the risk of dementia and AD, highlighting the changes in blood pressure from mid- to late-life and the interactions between vascular issues and neurodegeneration. Nonetheless, significant gaps still exist concerning the interconnected molecular pathways that relate to the severity of HTN, cerebrovascular impairment, and the specific pathology associated with AD.[6,7]

AD is a serious age-associated neurodegenerative disorder that poses a significant threat to public health, particularly among older adults. It is responsible for over 1.89 million deaths each year and contributes to an estimated $305 billion in healthcare costs.[7] The rising prevalence of this chronic illness in the elderly has become a major clinical concern. For instance, in 2019, approximately 6.5 million Americans aged 65 and older were living with AD or related dementias, resulting in 121,499 deaths. Unfortunately, no curative therapy currently exists, and available medications only provide temporary symptom relief.[8,9] The lack of effective disease-modifying treatments has contributed to increasing mortality rates, especially in low-income populations. Furthermore, the mechanisms underlying the onset of AD during midlife remain poorly understood.[10] Although prior reviews have generally emphasized the importance of antihypertensive treatment in reducing dementia burden, few studies have thoroughly examined how blood pressure-related vascular injury converges with AD-specific neuronal pathways to promote disease development.[11]

AD is the most prevalent neurodegenerative disease globally, affecting more than 30 million people and is characterized by extracellular amyloid plaques in the brain.[11,12] These plaques are mainly composed of the 4 kDa amyloid β peptide (Aβ), which is considered the primary pathogenic factor of the disease.[12] Aβ is a hydrophobic aggregation-prone peptide consisting of 38 to 42 amino acids. The cytotoxic nature of small Aβ oligomers triggers a cascade of pathological processes, including inflammation, suppression of hippocampal long-term potentiation, synaptic dysfunction, neurofibrillary tangle formation, neuronal loss, and ultimately the clinical manifestations and progression of the disease, leading to death.[13] The current analysis highlights AD-specific molecular pathways, such as amyloid-β dysregulation, tau pathology, oxidative stress, and blood–brain barrier disruption in the context of chronic HTN, in contrast to research that mostly focuses on vascular cognitive impairment.[13,14]

In this regard, AD is among the most difficult pathological frameworks for scientists worldwide.[14] AD is the most common kind of dementia in older adults, accounting for 60–80% of all dementia occurrences.[15] It is crucial to note that AD is typified by progressive neuronal brain and cognitive function losses.[16] Numerous risk factors, including oxidative stress, obesity, diabetes, high blood pressure, air pollution, smoking and high cholesterol, are important in both the development of AD and the creation of preventative strategies for it. Exercise and diet have been demonstrated to be protective factors that help prevent it.[17]

Since both HTN and AD are becoming increasingly common worldwide, researchers must understand their relationship.[18] Growing research suggests that long-term HBP accelerates neurodegenerative processes and damages the cerebral vasculature, which can lead to cognitive decline and the development of AD.[19] These disorders are linked by vascular dysfunction, impaired amyloid-β clearance, neuroinflammation and disruption of the blood-brain barrier (BBB).[20] Examining these relationships can yield important information about therapeutic approaches and early prevention tactics. To investigate the molecular links between AD and HTN, their combined effects on brain pathology, and new treatment approaches to address this dual burden, this review is necessary.

HTN differs from other risk factors due to its high global prevalence, modifiability, and direct impact on the vascular and neurodegenerative pathways in AD. This study adds value by offering an integrated view of the disease course, emphasizing prospective therapeutic approaches that have not been fully explored in prior studies, and meticulously linking HTN-induced vascular damage to AD-specific molecular pathways.

Neuropathology

Neuropathology provides important insights into the molecular and anatomical changes underlying AD. Aβ plaques, hyperphosphorylated tau-based neurofibrillary tangles (NFTs), synapse loss and neuronal degeneration are hallmarks of the neurodegenerative process.[21] Besides these basic lesions, ischemic infarcts, lacunes, cerebral hemorrhages, white matter lesions, cerebral amyloid angiopathy (CAA), BBB dysfunction, and microvascular fat degradation are all examples of vascular illness in the ageing brain and AD.[22] These vascular abnormalities, which are frequently seen in hypertensive and other vascular disorders, can cause cognitive impairment by interfering with the networks of neurons involved in executive functioning, memory and behavior. A growing body of research suggests that vascular damage brought on by HTN intensifies these neuropathological alterations, hastening neuronal death and tau or amyloid pathology.[23] Therefore, it is crucial to comprehend the overlap between vascular dysfunction and neurodegeneration to clarify the role that HTN plays in the development and progression of AD.

Hypertension Is a Risk Factor for Dementia and Cognitive Decline

Dementia significantly contributes to loss of independence and institutionalization in older adults, affecting approximately 5% of individuals over 65 years of age.[24] Its frequency increases dramatically with age, and by 2040, the number of dementia cases worldwide will increase to 81.1 million, up from 24.3 million in 2001. Significant increases are anticipated in developing nations such as China and India.[25] Given that dementia takes months or years to develop, even a slight delay in onset could drastically lower its frequency. Recent research has linked HTN to dementia and cognitive decline, indicating that blood pressure (BP) regulation may help prevent or delay the onset of dementia.[26]

Hypertension

Vascular dementia (VaD), AD and other cardiovascular diseases are significantly influenced by HTN, which is defined as blood pressure greater than 140/90 mm Hg.[27] Midlife HTN is significantly linked to subsequent cognitive decline, frequently preceding the onset of dementia by several decades. Numerous researchers have discovered connections between HTN and AD brain pathology.[28] Additionally, epidemiological studies have linked HTN to the development of AD. In AD patients' cross-sectional correlations between systolic blood pressure (SBP) and medial temporal lobe atrophy were discovered in brain imaging data.[20] In addition, hippocampal shrinking was observed in patients not receiving treatment for HTN in the Rotterdam and Honolulu-Asia studies.[29]

There is a complicated association between BP and cognitive function that changes with age and BP measurement. According to studies, elevated BP, including white coat and borderline HTN, has been linked to worse cognitive function in younger people, especially in memory and response time.[30] On the other hand, SBP has been associated with poorer

executive attention in older people over 70 years of age, indicating that maintaining ideal SBP levels is crucial for sustaining frontal brain functions. In very elderly people, including centenarians, low SBP and narrower pulse pressure have been linked to functional deterioration and worse cognitive performance.[26,30] Normal blood pressure generally appears to be associated with optimal cognitive performance across all age groups. Older people with low blood pressure may have underlying brain shrinkage, neuronal loss or problems with cholinergic neurotransmission. Moreover, a survivor group may have lower blood pressure and worse cognitive function as they age due to HTN-related death in younger patients, which could be an indication of reversed epidemiology.[31]

Long-term research also confirms that moderate cognitive impairment (MCI), dementia, particularly vascular dementia (VaD) and future cognitive decline are all significantly predicted by midlife HTN. Elevated SBP has been linked to reductions in naming, set shifting and visuomotor sequencing skills in individuals with MCI.[32] While the Honolulu Heart Program reported that 27% of dementia cases could be linked to untreated SBP above 120 mmHg in midlife, with even prehypertensive levels raising risk. Similarly, the Hoorn Study demonstrated that greater midlife SBP was associated with slower information processing speed 15 years later.[33] Furthermore, according to the Uppsala Longitudinal Study of Adult Men, it was found that elevated midlife SBP raised the chance of vascular and all types of dementia, especially when paired with other cardiovascular risk factors such as metabolic disorders and obesity. Since dyslipidemia and HTN often coexist, lipid abnormalities and the possible cognitive side effects of statin treatment in older people may have an impact on the relationship between HBP and cognitive decline, as in Figure 1.[34,35]

The impact of late-life BP on cognition remains debated. According to Women's Health and Ageing Study II, older adults over 70 with elevated high SBP or pulse pressure exhibited poorer verbal learning and executive function.[35] In a similar study, research conducted in Japanese and Korean populations has demonstrated that HTN raises the risk of vascular dementia; however, the correlation diminishes with age.[36] The highest rates of dementia progression were seen in older people with MCI who also had executive dysfunction and HTN. Interestingly, a decrease in BP often precedes the clinical onset of dementia.[37] This may result from Neuronal loss, cholinergic dysfunction in autonomic brain regions, or the consequences of reduced physical activity associated with cognitive decline.[38] Although the relationship in later life is more complicated, all the

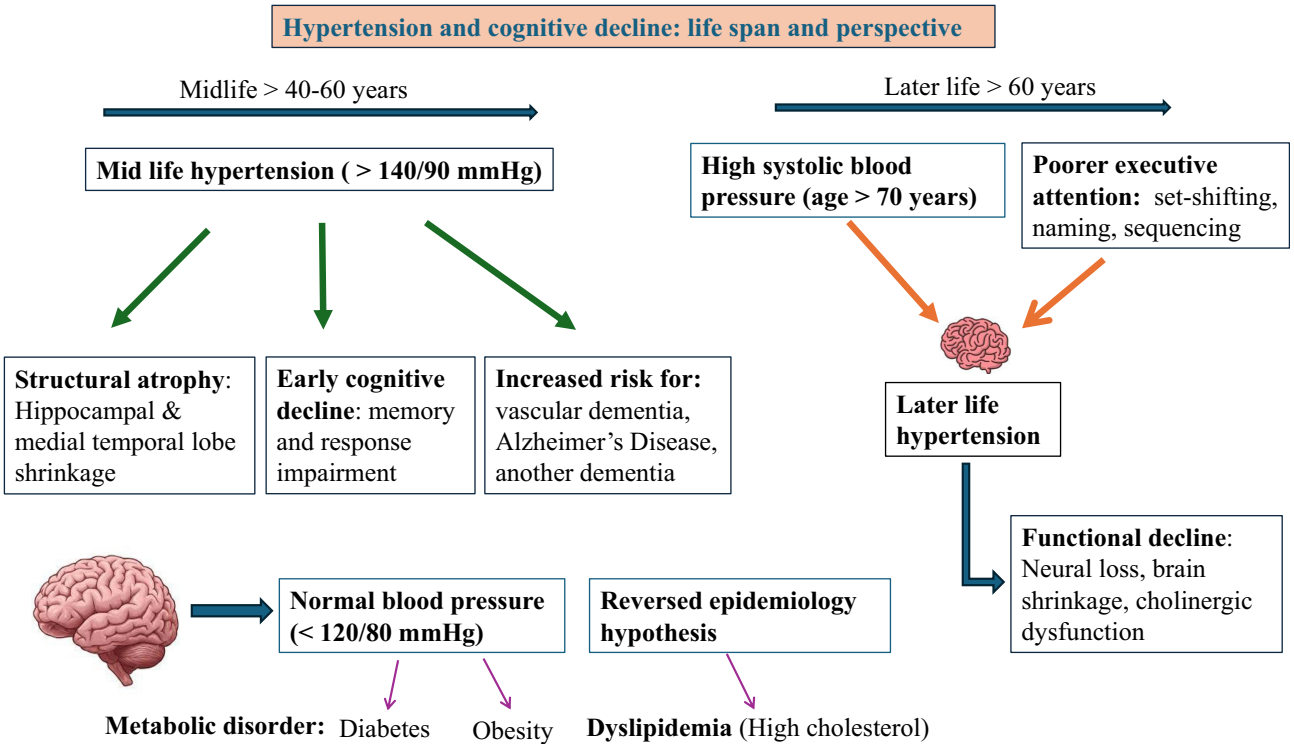


Figure 1 Risk of HTN and cognitive decline with life stages.

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evidence points to midlife HTN as a strong and consistent risk factor for eventual cognitive impairment. Maintaining optimal BP throughout adulthood and old age appears to be associated with long-term cognitive health.[39]

Midlife HTN is a broad and readily apparent risk factor for both cognitive decline and dementia, while the effects of late-life HTN are still unknown. The underlying biochemical process and effect of blood pressure variations in later life remain unclear, despite the extensive research linking the high midlife BP to brain shrinking, vascular damage and an increase in the risk of dementia. Future research should clarify the role of HTN in both tau and amyloid pathology and identify which blood pressure-lowering therapies provide the best cognitive protection.

Pathophysiological Processes Associated with AD and High Blood Pressure

Cerebrovascular Dysfunction

BP and age show different trends throughout life: systolic BP typically increases with age, but diastolic BP peaks around age 50 before starting to fall.[40] Ageing is a major factor in the development of HTN, as it raises blood pressure through behavioral and psychological processes in the brain.[41] Therefore, it is crucial to comprehend the relationship between HTN and cerebrovascular disorders and to discover common risk factors that lead to cognitive deterioration in the aged.[42]

Chronic HTN has been closely linked to dementia, stroke, cerebrovascular diseases, and cognitive decline. Both ageing and HTN have similar vascular consequences, especially in the cerebrovasculature, leading to structural alterations in blood vessels. Natural ageing itself raises blood pressure.[43] According to clinical evidence, the number of brain arteries decreases, and vascular walls thicken because of HTN. The pial and intracerebral capillaries become even more constricted as HTN progresses, especially in its later stages.[44] The brain's adaptive systems may eventually be overcome by ongoing exposure to these vascular changes, decreasing neuronal function and increasing the risk of primary dementia and cerebrovascular disorders, particularly stroke.[45]

According to the results shown in Figure 2, there is a strong correlation between HBP and age-related alterations in brain anatomy and function.[46] When taken as a whole, these findings suggest that HTN accelerates some aging-related changes in the brain and that its effects start long before clinical consequences like stroke become apparent.[47] Significantly, HTN-induced

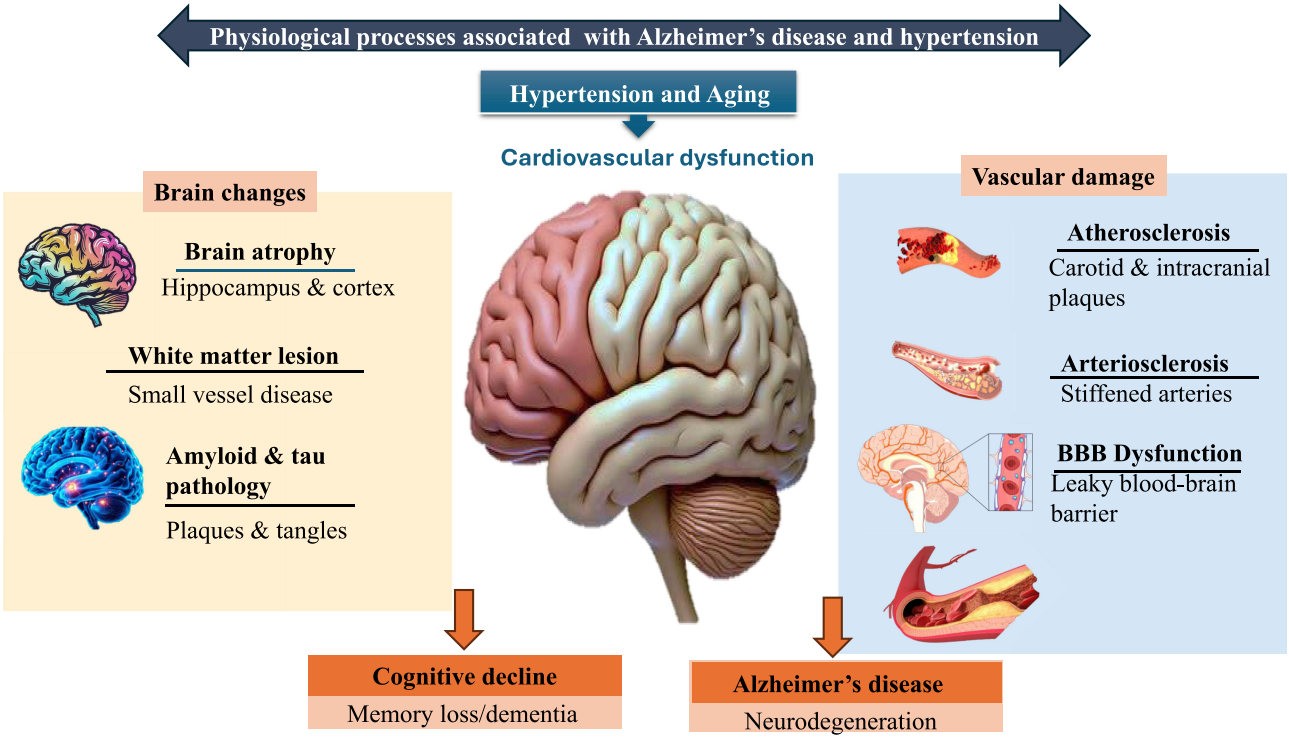

Figure 2 Pathophysiological processes between Alzheimer's disease and HTN.
Abbreviation: BBB, blood-brain barrier.

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cerebrovascular dysfunction directly causes AD by reducing cerebral blood flow, weakening the BBB and promoting Tau pathology and Amyloid-β accumulation. By promoting neuroinflammation and neuronal injury, these vascular alterations hasten cognitive decline and increase the risk of AD.

Changes in Brain Structure

Brain atrophy is a result of both ageing and HTN, especially in the inferior parietal lobule, entorhinal cortex, hippocampus, and prefrontal cortex.[48] HBP may lead to grey matter loss through both age-related and HTN-specific pathways. Aging mainly affects temporal and frontal areas, but HTN extends this impact to additional regions, such as the thalamus and supplementary motor areas.[49]

White matter decline, which typically manifests as white matter hyperintensities (WMHs) on brain scans and is strongly linked to HTN, is a common feature of ageing.[50] Death, dementia, stroke and cognitive decline are all predicted by these lesions, which are an indication of small artery disease.[51] HTN accelerates the development of WMH, particularly in the frontal lobe, by promoting inflammation, endothelial dysfunction and insufficient brain perfusion.[52] When BP is under control, this tendency is diminished, underscoring the need to control HTN. HBP and cognitive ageing are believed to be significantly mediated by WMHs, and related conditions like retinopathy and cerebral microbleeds also play a role in cognitive decline.[53]

It is remarkable that the hippocampus and entorhinal cortex, among other brain regions impacted by atrophy and white matter loss associated with HTN, are also early preferred targets in AD. Therefore, structural brain alterations brought on by HTN may worsen AD- related neurodegeneration and dementia progression, as well as reduce cognitive reserve.

Both Intracranial and Extracranial Cerebral Arteries

In both extracranial and intracranial cerebral arteries, HTN encourages the growth of atherosclerotic plaques, raising the risk of ischemic stroke.[54] While intracranial plaques affecting the circle of Willis and its branches are often more fibrous and may result in local arterial blockage, extracranial plaques, which are frequently found in the carotid and vertebral arteries, are rich in lipids and can cause artery-to-artery embolism.[55] It is believed that angiotensin II (AngII) has a role in endothelial dysfunction, neointima development and plaque progression by producing reactive oxygen species (ROS) and upregulating cytokines, chemokines and growth factors.[56] Furthermore, HTN causes arteriosclerosis or stiffness and constriction of the arteries, which lowers cerebrovascular reserve, increases mechanical stress on the microvasculature and decreases cerebral blood flow. Extracellular matrix remodeling, which includes collagen and fibronectin buildup, metalloprotease-driven elastin breakage and activation of pro-fibrotic pathways involving transforming growth factor-β (TGF-β), is mostly responsible for these structural alterations.[57]

AD is increasingly linked to cerebrovascular impairment and chronic HTN. Neurodegeneration can be exacerbated by increased tau pathology and amyloid-β deposition due to reduced cerebral perfusion, endothelial dysfunction, and microvascular damage.[58] Midlife HTN is associated with an increased risk of cognitive decline and dementia in later life due to the potential loss of neuronal integrity and synaptic function caused by the combination of vascular insufficiency and the neuroinflammatory milieu induced by HTN.[59]

Alzheimer's Disease with Chronic Hypertension

As was previously mentioned, the most important and controllable risk factor for cerebrovascular illnesses is HTN, which plays a major role in the development of dementia and stroke.[60] There is substantial evidence that high blood pressure and HTN are associated with higher risks of stroke, vascular dementia, and AD.[61] Hypertensive people frequently have pathological processes, including atherosclerosis and arteriolosclerosis, which cause stroke and cerebral ischemia and significantly impair cognitive function.[62] As shown in Figure 3, the clinical results also show that there is a complicated association between increasing HTN and cognitive function that varies depending on the patient's age and the stage of the disease. People between the ages of 65 and 75 have a particularly high risk of dementia, while people 75 and 85 or beyond have a less noticeable correlation.[63]

Clinical observations in AD patients further support this relationship; early-stage AD frequently manifests as high blood pressure, whereas late-stage AD is marked by more severe HTN along with notable cognitive impairment.[64] These results suggest that cognitive impairment associated with HTN advances more slowly in later life than in the early stages of old age.

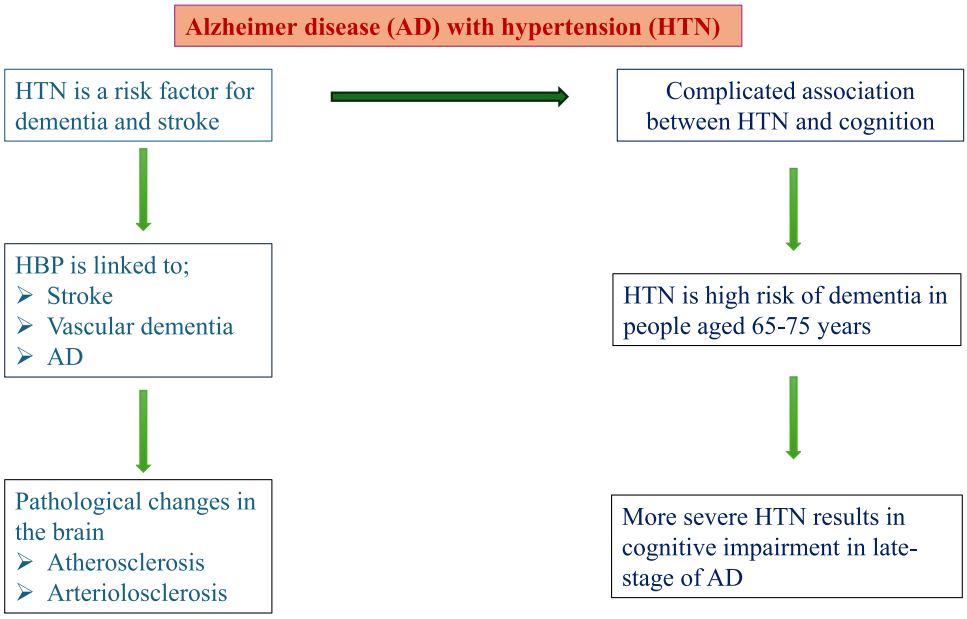

Figure 3 Association between Alzheimer's disease and HTN.
Abbreviation: HBP, high blood pressure.

Furthermore, research on female reproductive health and HTN shows that women are more vulnerable than men to early AD onset and HTN-related cognitive impairment.

Many aspects of the link between dementia and HTN are still unknown despite these findings.[65,66] Large-scale clinical investigations are needed to better understand the precise contributions of variables such as the severity, type (systolic versus diastolic), duration, and age of onset of HTN to the development of AD and vascular dementia.

Although the precise mechanisms are yet unknown, chronic HTN accelerates age-related vascular and brain changes that raise the risk of AD and cognitive decline. The impact of various BP patterns, medications, and sex variations on the advancement of dementia should be further investigated, and the development of early screening techniques may assist in detecting high-risk patients earlier.

Experimental Results on the Pathophysiology of HTN and AD

It is now widely accepted that microvascular abnormalities, such as cerebral artery constriction, are the main cause of the early stages of AD, due to the rapidly increasing evidence supporting the vascular theory of AD.[67] This viewpoint holds that one of the first and most important pathological indications in the development of AD is cerebrovascular dysfunction.[68] Numerous population-based cross-sectional and longitudinal studies have supported this theory by showing a substantial correlation between the incidence and progression of AD in older persons and vascular risk factors, especially HTN.[69] HTN is the most significant of these risk factors, being a significant factor that potentially doubles the risk of AD in older adults.[70]

The vascular hypothesis of AD has been expanded and refined by advances in experimental research examining HTN as a risk factor.[70,71] Notably, HTN speeds up microvascular damage, leading to several clinical consequences like cerebral microhemorrhages, disruption of the blood–brain barrier (BBB), and ensuing neuroinflammation, all of which are linked to the advancement of AD.[72] In both AD and HTN, neuroinflammation is a key factor. For example, research on Dahl salt-sensitive rats has demonstrated that long-term high-salt consumption can cause chronic neuroinflammation in the hypothalamic paraventricular nucleus, which can result in HTN.[73] On the other hand, HTN may exacerbate AD patients' cognitive impairment by increasing cerebral microvascular inflammation.[74]

According to the amyloid cascade theory, an excessive build-up of amyloid-beta (Aβ) causes multimodal microvascular damage, which advances AD disease and causes early cognitive deficits.[75] Numerous genetic and biochemical findings suggest the importance of Aβ synthesis, processing, and deposition inside neurons and cerebral microvessels in this process.[76] When the

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vascular and amyloid hypotheses are combined, it becomes clear that HTN exacerbates Aβ-induced microvascular damage, which worsens and speeds up the course of AD.[77] Chronic HTN increases amyloid deposition in cerebral microvessels, boosts beta-secretase activity, and encourages the cleavage of amyloid precursor protein (APP), according to experimental research employing transgenic animal models infused with angiotensin II.[74,75,78] Like this, transverse aortic coarctation-induced HTN in mice increases Aβ accumulation and causes early cognitive deterioration; molecular alterations can be seen as soon as four weeks after HTN onset. These results suggest that cerebrovascular damage can be caused solely by HTN.[79]

Furthermore, it has been discovered that both ageing and HTN increase the expression of amyloidogenic genes in the brain, and that HTN-driven AD pathogenesis is further aided by the activation of receptors for advanced glycation end-products (RAGE) within cerebral microvessels.[80,81] The therapeutic potential of focusing on these pathways to reduce microvascular dysfunction and postpone the onset of AD is highlighted by this mechanism.[82]

Tau aberrations, together with Aβ pathology, play a significant role in AD. Although research is still underway, emerging evidence connects HTN to tau hyperphosphorylation and misfolding. According to data from the AD Neuroimaging Initiative, hypertensive individuals with lobar microbleeds exhibit faster cognitive decline, which may be associated with altered tau pathology, as reflected by lower cerebrospinal fluid phosphorylated tau levels, potentially indicating reduced tau hyperphosphorylation or disturbances in tau clearance linked to cerebrovascular injury.[83] Animal studies indicate that HTN causes cerebral small vessel disease (CSVD), which is linked to higher Aβ and tau levels.[84] Telmisartan has been demonstrated to lower Aβ deposition, tau phosphorylation, and neuroinflammation, providing a treatment option. Furthermore, clinical data in AD and progressive supranuclear palsy (PSP) patients suggest that abnormal tau accumulation is a common pathogenic characteristic.[85]

Collectively, these findings illustrate the complex relationship between HTN severity and AD pathogenesis. They provide critical insights for constructing integrative models that connect clinical and experimental data, bolstering the idea that HTN in older persons is a fundamental trigger for the start and progression of AD, as in Figure 4.[77,86]

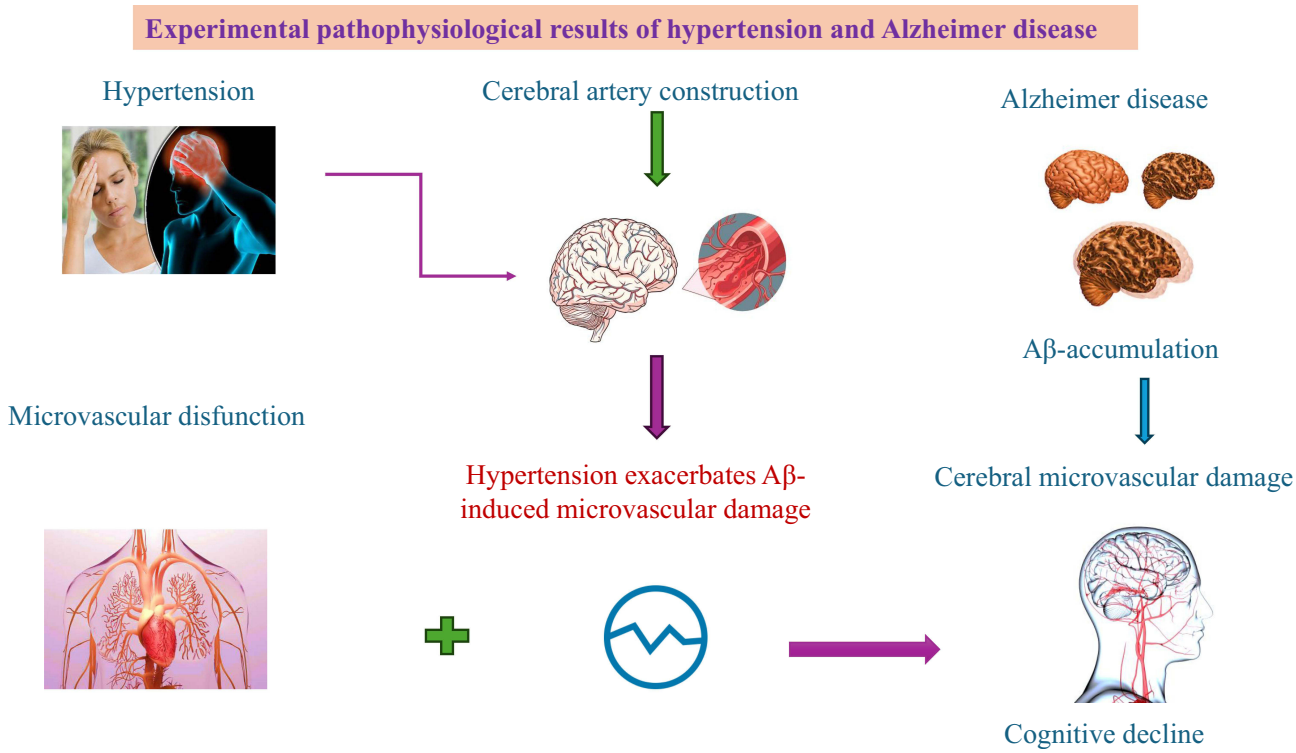

Figure 4 An explanation of the pathophysiological relationship between Alzheimer's disease (AD) and hypertension (HTN).

Biomarker Confirmation of AD Pathology in a Hypertensive Patient

Significant evidence indicates a link between high blood pressure and AD; however, the fundamental processes are still not well understood.[86] Current studies seek to understand if high blood pressure is a direct factor in the changes associated with AD or whether it plays a role in speeding the cognitive decline.[87]

To investigate molecular markers linking HTN and AD, researchers use physiological measurements such as blood pressure and CSF analysis, as well as clinical imaging techniques such as PET and MRI.[88,89] There is evidence that people with HTN have greater levels of brain amyloid in older people with vascular risk factors. This suggests that elevated amyloid accumulation may be directly associated with late-life HTN, but further investigation is needed to confirm this.[90] Research of people over 60 using PET (for tau and amyloid) and MRI found that higher vascular risk, particularly HTN, is associated with brain atrophy and neurodegeneration, not increased amyloid buildup.[91] Although blood pressure is crucial to monitor, there was no correlation between late-life BP and brain amyloid levels. However, higher systolic blood pressure was associated with more neurofibrillary tangles[92] (Figure 5).

HTN is not linked to amyloid, but it is associated with tau in APOE-4 homozygotes, suggesting a probable connection between blood pressure and APOE genotype.[93] HTN is also linked to localized brain atrophy, suggesting that it may contribute to AD-related neurodegeneration. MRI results also reveal that greater midlife blood pressure is linked to hippocampus shrinkage, particularly in people with untreated HTN.[94]

Medication for Hypertension and Alzheimer's Disease

Antihypertensive medicines (AHDs) are commonly used to treat and control high blood pressure (HBP), but accumulating clinical evidence suggests that they may also lower the risk of dementia and AD.[95] Studies on HTN and late-life cognitive decline suggest the use of AHDs to reduce the risk of dementia. Extensive clinical trials suggest that reducing

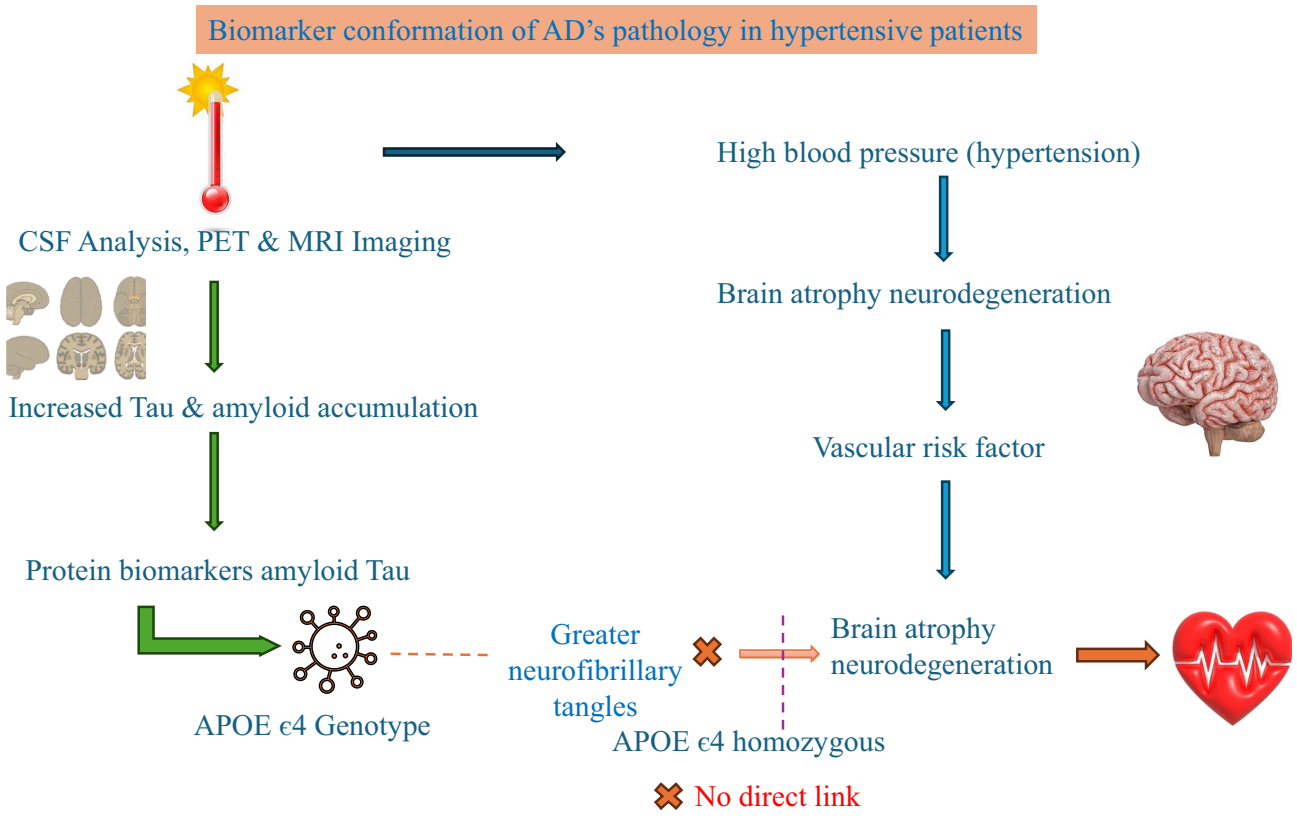

Figure 5 Biomarker conformation of AD's pathology in a hypertensive patient.
Abbreviations: CSF, cerebrospinal fluid; PET, positron emission tomography; MRI, magnetic resonance imaging; APOE, apolipoprotein E.

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systolic blood pressure below 120 mmHg, rather than 140 mmHg, dramatically decreases the chance of mild cognitive impairment and dementia.[96]

Currently, AHM is being used in clinical trials to treat dementia and AD-related illnesses. Additionally, the effectiveness of the AHM drug in reducing the risk of AD is being studied.[97] Researchers explore the relationship between AD and AHM therapy, which identified four major drugs used.[98] These include CCBs and angiotensin-converting enzyme inhibitors, Angiotensin II receptor blockers (ARBs), beta-blockers, and ACEIs, which are the four primary kinds of AHM drugs.[99] Recent years, several excellent meta-analyses have been conducted. Most of them focused on one element of BP, particularly the use of AHMs, and one cognitive outcome, which led to uneven outcomes.[100,101]

Multifunctional Imaging Methods in AD and HTN

The development of multimodal imaging techniques has improved our understanding of the pathophysiology underlying the imaging characteristics of AD and HTN, such as atrophy, WMH, and cerebral microhemorrhages.[101] Since AD patients have higher ADC in the temporal lobe and hippocampus and lower FA in multiple brain regions, diffusion tensor imaging (DTI) may give a more objective way to distinguish between VaD and AD. Specific patterns of white matter alteration, such as Para-hippocampal tract involvement in AD and thalamic radiation involvement in VaD, further support this differentiation.[100,101] According to the "vascular dysregulation hypothesis," which contends that reduced blood flow aggravates AD and ADRD, cerebrovascular dysfunction linked to HTN contributes to AD pathogenesis. Cerebrovascular dysfunction can be used as a diagnostic sign and target for treatments because it happens early. Although DTI, fMRI and PET each have drawbacks despite their benefits, multimodal imaging nonetheless makes it easier to investigate connections between AD and HTN.[102]

Conclusion, Observation and Future Perspective

The pathogenesis of AD and HTN is complex and closely related. Overall, this review highlights HTN as a major and modifiable risk factor that critically contributes to the development and progression of AD. There is mounting evidence that chronically high blood pressure accelerates vascular dysfunction, neurodegenerative processes, and anatomical changes in the brain that result in cognitive decline. The effects place HTN at the center of the mechanistic link between vascular pathology and neurodegeneration. Specifically, midlife HTN is a strong and accurate predictor of late-life dementia and affects amyloid-β accumulation, tau pathology, cerebrovascular remodeling and white matter damage. This interaction between HTN and core AD hallmarks underscores its pivotal role in disease initiation and progression.

Neuropathological and experimental findings consistently support the vascular theory of AD by demonstrating that HTN-induced endothelial degradation, microvascular dysfunction, inflammation and reduced cerebral perfusion significantly worsen AD-related pathology. Collectively, these mechanisms illustrate how vascular injury driven by HTN amplifies classical AD's pathology. Biomarker studies demonstrate that HTN is associated with tau burden, neurodegeneration and localized brain atrophy even when amyloid accumulation remains unchanged. These observations further emphasize the strong interaction between vascular dysfunction and neurodegenerative processes in AD. Antihypertensive drugs, particularly those that target the renin-angiotensin system, have demonstrated promise in lowering dementia risk and AD-related pathology, highlighting the therapeutic importance of maintaining optimal blood pressure control throughout adulthood. This supports the concept that HTN represents a clinically actionable therapeutic target in AD. By identifying common imaging indicators such as WMH, microbleeds, and atrophy, and by demonstrating that HTN accelerates the morphological and functional changes in the brain associated with AD, multimodal imaging advancements support these findings. Together, these imaging and biomarker data provide converging evidence linking HTN to AD- related brain injury. When taken as a whole, these findings demonstrate that managing HTN is a significant and adaptable tactic for lowering the prevalence of dementia worldwide and delaying the progression of AD. In summary, this review integrates mechanistic, clinical, imaging, and therapeutic evidence to establish HTN as a central driver of AD risk.

The specific HTN patterns, molecular pathways and antihypertensive medication classes with the greatest neuroprotective effects, especially those that target the renin-angiotensin system, should be the focus of future research. Clarifying these interactions will further strengthen the vascular model of AD. The vascular model of AD will gain more traction if it becomes clear how blood pressure control affects amyloid and tau pathology, cerebrovascular integrity and long-term cognitive

outcomes at various periods of life. Given the circumstances, maintaining ideal blood pressure throughout adulthood continues to be a critical tactic for protecting brain function and lowering the prevalence of AD worldwide.

Summary

This review emphasizes the close connection between AD and HTN, demonstrating how long-term high blood pressure hastens vascular dysfunction, tau and amyloid-β pathology, and cognitive loss. Although the evidence well supports the vascular theory of AD, some studies suggest weaker or indirect effects of HTN, and results may differ by age, sex, or other medical factors. Although some trials have been equivocal, antihypertensive drugs, particularly those targeting the renin-angiotensin system, may have neuroprotective effects. In general, controlling blood pressure throughout life remains a viable way to lower the risk of dementia; however, more research is needed to determine which HTN patterns and treatments offer the greatest protection.

Abbreviations

AD, Alzheimer's disease; HTN, hypertension; HBP, High Blood Pressure; BP, Blood Pressure; SBP, Systolic Blood Pressure; BBB, Blood Brain Barrier; AHDs, Antihypertensive drugs; Aβ, Amyloid-β; WMH, White Matter Hyperintensities; DTI, Diffusion Tensor Imaging; fMRI, Functional Magnetic Resonance Imaging; PET, Positron Emission Tomography; NFTs, Neurofibrillary tangles; CAA, Cerebral Amyloid Angiopathy; APP, Amyloid Precursor Protein; TGF-β, Transforming Growth Factor-β.; Vad, Vascular dementia; MCI. Moderate Cognitive Impairment; ROS, Reactive Oxygen Species; RAGE, Receptor for advanced glycation end-products; CSVD, Cerebral Small Vessel Disease; CSF, Cerebrospinal fluid; APOE, The apolipoprotein E; ARBs, Angiotensin II receptor blockers.

Author Contributions

All authors made a significant contribution to the work reported, whether that is the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revision or critical reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

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Disclosure

The authors report there are no conflicts of interest in this work.

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