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Vascular Dementia: A Revision

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Abstract

The prevalence of Alzheimer disease, a degenerative dementia, in North America is approximately twice the worldwide average. Alzheimer disease's range is somewhere between 60 to 80 percent of all cases of dementia, whereas 15 to 34 percent of dementia cases exhibit significant vascular pathology during postmortem neuropathological examination. Prolonged persistence of reduced blood flow and microscopic bleeding in brain tissue lead to vascular dementia. The etiology and pathogenic mechanisms for vascular dementia are still an enigma, although the impaired cardiovascular and cerebrovascular systems are thought to play a role. Vascular dementia is classified as cognitive impairment induced by either cardiovascular disease, ischemia, or hemorrhagic brain injury. The vital role of both the cardiovascular and cerebrovascular system is to maintain a relatively smooth blood flow through capillaries, which infiltrate every tissue and every cell in the body. Brain capillaries are capable of adjusting blood flow to meet the metabolic needs of the brain in response to neural activity. The circulatory system has the capability to minimize functional diffusion distance within tissues. The central nervous system and endocrine system assist in making constant adjustments to the blood flow as conditions change in tissues and cells. An increase in diffusion distance or alterations in the structure of the arterioles, an important vascular resistance site within the entire vascular network, in response to long-term physiological alterations in blood flow brought about by chronic disease may be the first manifestation of the breakdown of nerve cells. Accordingly, the purpose of this review is to offer a hypothetical link between persistent peripheral cardiovascular-related diseases and vascular dementia and will present potential mechanistic connections underlying observed effects.

Keywords: Alzheimer disease; Dementia; Vascular dementia; Kallikrein-kinin system (KKS)

Introduction

Alzheimer's disease (AD) is an age-associated neurodegenerative disease [1,2]. Elderly people experience cognitive decline due to an array of reasons [3] including impaired vascular mechanisms [4]. A widespread increase of AD incidence [5] and vascular-induced dementia demands for an urgent development of effective therapeutic strategies.

The population-based Rotterdam Study without dementia provides evidence that lower cerebral perfusion is linearly associated with higher risk of dementia [6]. In a recent large population-based study, a favorable cardiovascular health is found to be related to a lower risk of dementia in older age [7]. Vascular disease affects cognition [8]. While vascular brain lesions lower the threshold of AD pathology [9,10], AD pathology can cause an increase in the risk of dementia after stroke [11]. Activation of endothelial cells (EC) is the key step not only during neural demyelination of the CNS [12] but also AD pathogenesis [13]. Uncontrolled activated EC of the cerebrovasculature [14] is emerging as an important risk factor for AD in humans and AD in transgenic animals [15].

Vascular dementia (VD) is a central nervous system disease with cerebral small vessel disease and neurodegenerative components. It encompasses a spectrum of cognitive deficits from mild cognitive impairment to dementia. The prevalence of cerebrovascular disease, vascular pathology and vascular risk factors in a wide range of neurodegenerative diseases have been reported [1,9]. Evidence clearly indicates that vascular risk factors are independently involved in elevated risk of Alzheimer's disease [16]. Thus, we review the clinical relevance of the vascular changes during systemic inflammation and cerebrovascular inflammation in the context of clinically-apparent diseases such as impaired cognitive behavior and neurological conditions as Alzheimer's disease. In particular, we review emerging evidence for the following concepts: (1) the contribution of kallikrein-kinin system (KKS) changes induced by chronic diseases to progression of the cerebrovascular disease process, and (2) the KKS dysfunction may be an integral part of cerebrovascular pathogenesis, contributing to the onset and development of vascular dementia, inflammatory response, and breakdown of blood-brain barrier (BBB).

Age-related metabolic diseases such as diabetes and elevated blood pressure have the potential to elicit uncontrolled perturbation of vascular wall elements (Figure 1). When the antithrombotic and anti-inflammatory properties of endothelium of blood vessels are compromised, a sequestered microenvironment is created, which increases hyper-adhesivity of endothelial cells to the components of plasma kallikrein-kinin system (KKS) in addition to the inflammatory cell-endothelial cell interaction. The plasma KKS is activated, thereby the proteases of KKS exert their full prothrombotic and proinflammatory potential at the vessel wall. High plasma kallikrein, a protease of KKS, activity is associated with higher blood pressure and diabetes. It is well-established that a normal thrombotic response or inflammatory response does not result in vascular dysfunction,

suggesting that the host has ways to control this potentially injurious process.

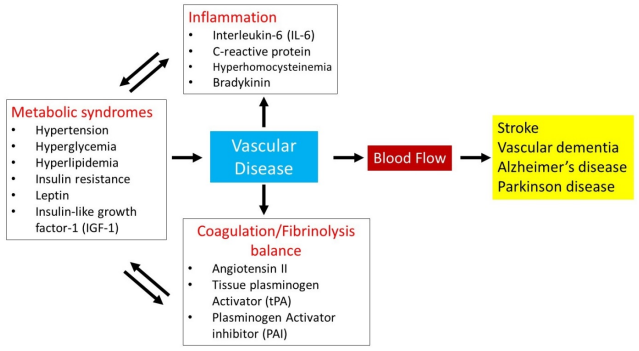

Figure 1: Schematic interpretation of cardiovascular and cerebral small vessel diseases and the risk of vascular dementia

There are many risk factors associated with vascular dementia. Many patients with vascular dementia experience more global symptoms such as diabetes, hypertension, and cognitive changes. When diabetes or hypertension coexist with other cardiovascular risk factors, the relationship between metabolic syndromes and vascular dementia becomes evident. The risk for vascular dementia apparently increases over time as the number of metabolic syndromes accumulates. In addition to inflammatory lesion formation, the KKS dysregulation can accelerate cerebral vessels to leak leading to progressive loss of structure or function of neurons. The brain KKS dysfunction may also cause atherogenesis leading to dementia of both Alzheimer's and vascular dementia. The KKS-induced neural atrophy, an indicator of neurodegeneration, can silently begin early in the disease course and drives disability over time. The majority of patients with vascular dementia due to repeated ischemic attacks demonstrate disease progression characterized by insidious cognitive decline from the outset.

Evidence indicates that vascular dementia may result from a combination of genetic predisposition and environmental influences [17]. Established environmental risk factors for vascular dementia include heavy metals [18], lithium exposure [19], and viral exposures [20]. However, there is significant variability among patients with vascular dementia regarding clinical disease course. Further investigations are needed to determine the modifiable environmental factors that might be manipulated to positively influence outcomes once the diagnosis of vascular dementia has been recognized. Among the above risk factors, metabolic syndromes and viral exposure for vascular dementia development have also been demonstrated to impact clinical course. Nevertheless, a significant portion of environmental risk for the development of vascular dementia currently remains unexplained. While large-scale clinical trial data is not yet available, a growing body of literature including epidemiologic, preclinical, and observational studies as well as small clinical trials suggests the importance of dietary factors in the risk of impaired neurocognition onset and clinical course [21,22]. This review will begin with a discussion of vascular architecture, the components of the plasma KKS, and potential underlying mechanisms for the effects of KKS as a disease modifier followed by a presentation of the current literature on metabolic syndromes in vascular dementia. Potential effects of KKS on vascular dementia symptoms will also be discussed.

Cerebral Blood Flow Regulation

Cerebral blood flow is dynamically controlled by the components of the neurovascular unit (NVU) including endothelial cells, pericytes, smooth muscle cells (SMCs), astrocytes, oligodendrocyte progenitor cells, and neurons [23-25]. Evidence shows that pericytes are capable of constricting brain capillaries under pathological conditions such as ischemic stroke [26], AD [27-29], and vascular cognitive impairment [30].

The current view of cerebral blood flow (CBF) dynamics suggest that arteriole and capillary diameter are differentially controlled by smooth muscle-covered arterioles or pericyte-covered capillaries [25,31]. Neuronal activity is found to alter capillary diameter in order to control CBF, whereas SMCs located at arterioles control CBF. However, evidence indicates that arteriolar SMCs may be the key players regulating CBF [31]. There is also suggestion that the pericytes residing at the proximal capillaries, as gatekeepers, possess both characteristics of pericytes and SMCs. The aforementioned studies suggest that redundant mechanisms operate to regulate CBF. Studies also show that the blood vessel dilator factors including the bradykinin-related mediators, namely prostanoids and nitric oxide, and histamine can counteract the constrictor effects of norepinephrine in the cerebral circulation. At the most fundamental level, CBF regulation is influenced by a diverse array of factors including cardiac output, cerebrovascular autoregulation [32], and neurovascular coupling [33,34]. To have normal brain function, adequate CBF is maintained by perfusion pressure [35] and mediated by chemical agents such as nitric oxide (NO), eicosanoid products, endothelins, and adenosine to prevent ischemia-induced brain injury.

Common Denominator among AD, Cerebrovascular and Cardiovascular Diseases

Uncontrolled chronic hypertension is a common risk factor for cerebrovascular disease [36], which is associated with considerable mortality and morbidity. Chronic hypertension can lead to a constellation of abnormalities that includes a thickening of vessel walls, reduced vessel elasticity, and the narrowing of the lumen, especially in small vessels. The mechanisms responsible for progression to abnormalities of blood vessels include a response to the mechanical stress from elevated blood pressure, imbalance autocrine and paracrine signaling, a persistent locally-produced inflammatory mediator, and the influences of neurohormones [37]. Alterations in the extracellular matrix [38] are critical triggers of the vascular malformations. There is widespread agreement that reduced vessel elasticity along with a reduction in blood flow are important intermediate phenotypes in the progression of both AD and cerebrovascular disease [16] and cardiovascular disease and is associated with adverse outcomes. The progression from chronic hypertension and reduced vessel elasticity is an important step on the pathway toward not only heart failure but also a reduction in blood-brain barrier (BBB) integrity, which can result in both cerebral edema and the introduction of systemic elements into the brain parenchyma. Pathological changes present in patients with uncontrolled hypertension includes a decrease in hippocampus volume, which is typically associated with a higher risk of developing clinical AD.

Long-term research studies have shown that hypertension is a risk factor for dementia, vascular aging, stroke, particularly vascular dementia [39]. Studies have found that the risk of dementia and AD varies dramatically between individuals, even among hypertensive patients due to interindividual variability in the reduction of vascular elasticity in response to hypertension. It seems likely that a genetic variation or genetic drift exits. There is considerable interest in identifying the candidate gene(s) *via* the use of microarray data and genome-wide association studies. However, the findings of these studies remain in their relatively early stages. Conversely, there is evidence demonstrating that inflammation [40], stroke [41] and hypotension [42] are closely associated with a risk of AD and vascular dementia (Figure 1). Notably, increasing age, diabetes mellitus, and obesity are also associated with a reduction in vascular integrity [43]. While diabetes mellitus triggers arterial stiffening and narrowing of the arterial wall, obesity is characterized as a volume-overload state. Several studies have demonstrated that pharmacological control of hypertensive [39] and diabetic are associated with reduced risk of clinical events including cardiovascular death, stroke, AD, vascular dementia [41]. Taken together, the joint influences of lifestyle changes, medications to effectively control hypertension and hyperglycemia, should help to retain or improve cognitive function by reducing the risk of AD and/or vascular dementia.

Kallikrein-Kinin-System

Kininogen

Kininogens, as carriers of kinins, perform a broad spectrum of physiological effects, in particular, many proinflammatory functions. There are two isoforms of kininogen, designated low (70 kDa) and high (120 kDa). LK and HK are encoded by a single gene [44] on human chromosome 3q26. Differentially spliced kininogen isoforms (LK, HK) exert distinct biological functions. Their susceptibility to cleavage by plasma and tissue kallikreins are different. Plasma kallikrein releases bradykinin from HK, while tissue kallikrein prefers to release kallidin from LK. Both LK and HK are present in extracellular fluid compartments, HK is also found in the cerebrospinal fluid.

HK has a variety of combinations of functions including antithrombotic, profibrinolytic, antiadhesive, and antiangiogenic actions [45]. HK consists of two unequal long polypeptide chains, composed of both distinct functional and structural units. These chains designated heavy and light. The heavy chain (domains D1 to D3) and the light chain (domains D4 and D6) are connected by a linker. Domain D4 of kininogen has the bradykinin (BK) sequence, a unique domain, which is not shared by any other members of the blood coagulation proteins. Bradykinin exerts its antithrombotic and profibrinolytic properties by inducing release of nitric oxide and tissue plasminogen activator from endothelial cells (Figure 1). The three cystatins, cysteine protease inhibitor, domains of kininogens [46] play a vital role in the control of inflammation and embryogenesis [47,48].

The binding of HK to endothelium is a critical step in the generation of bradykinin. While this recruitment process is not yet defined, the requirement for specific cell-surface membrane proteins in the binding of HK to endothelial cells have been elegantly demonstrated using a variety of experimental approaches. The current paradigm for HK recruitment is that following endothelial cell activation, HK binds to cell surface binding receptors through the HK-binding domain 3, domain 5, or both. Direct visualization of the HK binding to cells has revealed that HK binds the endothelial cells, platelets, neutrophils, or astrocytes through one or more receptors like globular complement 1q receptor (gC1qR) [49], urokinase plasminogen activator receptor (uPAR) [50], and cytokeratin 1 [51]. Bradykinin is released from the HK by plasma kallikrein following HK binding to activated endothelial cells allowing the binding of bradykinin to bradykinin B2 receptors. The persistent recruitment and metabolism of kininogen levels during vasovagal, septic and anaphylactic shocks, carcinoid syndrome flush, and dumping syndrome results in dramatic consequences that include a decrease in HK and kallikrein. Thus, HK intimately involved in inflammation.

Low level of kininogen is detected in many areas of the brain including in pituitary, choroid plexus, cerebellum, medulla oblongata, hypothalamus, striatum, midbrain, hippocampus, and cerebral cortex. However, the tight regulation of HK expression is disrupted after mechanical trauma, inflammation and infection [52]. The chemical composition of cerebrospinal fluid reflects and affects the neural tissue. Normally, no HK is present in cerebrospinal fluid. However, high levels of HK are found in the cerebrospinal fluid of patients with Alzheimer's disease and systemic lupus erythematosus [53].

Plasma prekallikrein (PK, Fletcher factor)

Human plasma prekallikrein (PK), a key regulator of bradykinin generation, and HK generally circulate as a noncovalent complex in the blood, with HK basically serving as a chaperone for PK. The gene encodes PK is located on chromosome 4. PK is a multifunctional protein and a serine protease [54]. PK is primarily synthesized in the liver and is secreted into the plasma. However, plasma kallikrein mRNA is expressed significantly in pituitary, choroid plexus, cerebellum, medulla oblongata, hypothalamus, striatum, and midbrain and moderately in hippocampus, and cortex [54]. The plasma concentration is about 490 nM and most of the plasma prekallikrein (90%) circulates bound through its domain 2 to the domain 6 [55] of high molecular weight kininogen. Prekallikrein has 58% structural similarity to human factor XI [56]. Factor XI also binds to HK [57].

Factor XII (FXII, a plasma protease known as Hageman factor) has been the focus of intense worldwide research from the standpoint of blood coagulation and peripheral edema. Activation of this zymogen is modulated by a number of efficient protective mechanisms. These include the normal intact endothelium, the endogenous inhibitors of activated FXII (FXIIa) and hepatic clearance of FXIIa. Activation of FXII is characteristically seen during pathophysiological conditions and is triggered in response to a host of diseases ranging from the benign to the potentially life threatening. FXIIa activates two catalytically distinct blood coagulation proteins, designated as factor XI (plasma thromboplastin antecedent) and prekallikrein (PK), which are important in blood clot forming cascade, proinflammatory bradykinin (BK)-related peptides (kinins), and the release of both TNF and IL-1β (Figure 2). Importantly, all of the contact-stimulated BK production is abolished in FXII knockout mice. This observation suggests a pivotal role for FXII in the local regulation of BK (Figure 2).

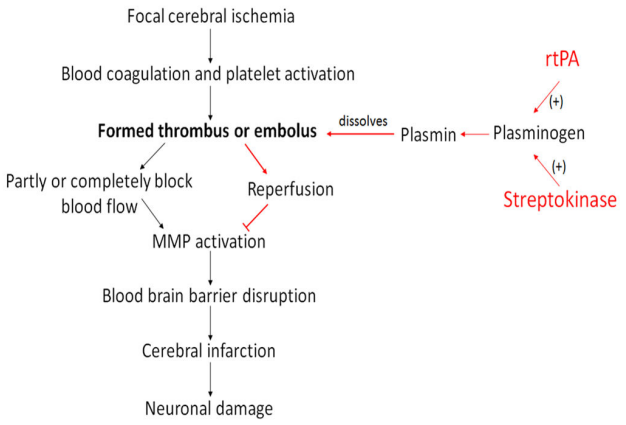

Figure 2: This scheme represents a balance between the procoagulant-dependent clot forming cascade and the fibrinolytic system that is responsible for dissolving the formed thrombus or embolus. Imbalance of the blood coagulation process tilts toward blood clot formation or bleeding. Temporary blockage of blood flow in an artery within the brain caused by circulatory conditions such as plaque, thrombus or embolus, is a major contributor to neuronal damage in cerebral ischemia. This blockage can appear at the neck or in the brain tissues. Clot lysis is attained by the direct action of plasmin, a fibrinolytic protease. Plasmin is formed through proteolytic cleavage of its inactive zymogen, plasminogen. Tissue plasminogen activator (tPA) and urokinase type plasminogen activator (uPA) are the known physiological activators of plasminogen. Recombinant tPA (rtPA) and streptokinase (SK) are the non-physiological thrombolytic agents.

Prekallikrein can be converted to kallikrein by prolylcarboxypeptidase (PRCP). PRCP is present on endothelial cell surface and is primarily responsible for prekallikrein activation in the absence of factor XIIa [58]. Prekallikrein can also be activated to kallikrein through autoactivation, but the process is slow [59] and is necessary to initiate the coagulation process in the plasma.

Kallikrein catalyzes HK to release bradykinin and cleaved HK (HKa). Kallikrein can induce the aggregation of neutrophils and secretion of neutrophil elastase. Kallikrein also modulates fibrinolysis and complement system [60]. Conversely, C-1 inhibitor, a member of complement system, reduces kallikrein action and subsequent bradykinin formation. Kallikrein or activated factor XII, a kallikrein substrate, converts plasminogen to plasmin [61]. Plasmin breaks down fibrin to fibrin end products.

Plasma prekallikrein deficiency can be identified with activated partial thromboplastin time (APTT). Patients with prekallikrein deficiency are asymptomatic. However, these patients exhibit prolonged APTT.

Inhibiting KKS activity as a specific mechanism for potentiating the effects of existing anti-inflammatory therapies in AD.

The mechanism by which KKS influences cognition and AD risk remains under active investigation. One mechanism may be through kallikrein-[62] or BK-dependent processes [63]. Bradykinin B2 receptors are present in the cardiovascular and cerebrovascular systems. Immunostaining studies indicate that the B2 (B2) receptor is abundant in the endothelial linings of the aorta, other elastic arteries, muscular arteries, capillaries, venules, and large veins, where it localizes preferentially to the luminal face of the endothelial cells. However, B2 receptors are prominently found in the perivascular smooth muscle cells of the tunica media of small arterioles (i.e., the principal blood-pressure regulating vessels) of the mesenterium, heart, brain, and kidney. Owing to the nature of plasma KKS signaling, regulation, and its autoactivation on negatively charged surfaces, strategies to inhibit kallikrein and factor XII actions are being pursued as potential adjunctive measures for treating diseases such as stroke, hereditary angioedema, and thrombosis.

Cerebrovascular unit possesses B2 receptors and conditions in the experimental cerebral ischemia microenvironment can lead to enhanced responsiveness to bradykinin [63]. Recent studies have shown associations between changes in plasma BK and increased AD risk in humans. The association between vascular dysfunction and KKS activation in AD pathogenesis is reported [64]. Although they frequently co-occur, vascular injury and KKS activation are widely accepted as important independent risk factors for local inflammation state. Therefore, inhibiting BK-induced B2 pathway has been proposed as a specific mechanism for potentiating the effects of existing anti-inflammatory therapies or for directly inhibiting the constrictor effects of norepinephrine.

Thrombus formation and degradation

Acute ischemic stroke (AIS) and cerebrovascular disease are among the top five leading cause of death in the United States. Brain ischemia is a condition by which a prominent cessation of blood flow to the brain, leading to necrosis and apoptosis. Although the current therapeutic targets of AIS are BBB disruption, oxidative stress, inflammatory reaction, and neuronal apoptosis, numerous central nervous system diseases are linked to disruption of the BBB that can lead to changes in permeability and perturbation of biochemical and biomechanical signaling between the vascular system and the neurons.

Fibrin and/or fibrinogen deposition are involved in a whole range of pathogenic conditions such as acute ischemic stroke (AIS) and Alzheimer's Disease (AD) [65-67]. Enhanced cerebrovascular fibrin deposition contributes to impaired vascular barrier properties and resultant neuronal injury during AIS pathogenesis and the progression of neuronal dysfunction. It is well-established that AIS-induced reduction of blood flow in the brain tissues leads to neuronal degeneration, which takes from a period of hours to days. Recombinant tissue plasminogen activator (rtPA), a thrombolytic therapy, is of proven to have a propensity to improve and resolve neurologic deficits in some select patients with AIS, if this treatment is administered within the first 3 hours of ischemic stroke onset.

The fibrinolytic system controls dissolution of the fibrin blood clot [68]. Clot lysis is attained by plasmin *via* proteolytic cleavage of its inactive zymogen, plasminogen. Tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPA) are the physiological activators of the fibrinolytic pathway (Figure 1). Our lab has characterized specific interactions of the plasma kallikrein-kinin system component with fibrinolytic system component, importantly serve to localize and fine-tune the process of plasmin generation. Both tissue plasminogen activator (t-PA) and its endogenous inhibitor, plasminogen activator inhibitor type 1 (PAI-1), are involved in thrombus formation and degradation. Vascular fibrinolytic balance is achieved by the competing effects of t-PA and PAI-1 [69]. Altered

levels of tPA or PAI-1 are risk markers for cardiovascular disease. Factors that cause elevation of PAI-1 levels and induce reduction in t-PA levels may increase the risk of thrombosis. While the activation of the renin-angiotensin promotes PAI-1 production [70], bradykinin-mediated B2 receptor activation results in t-PA generation [71]. Evidence angiotensin II, a major effector of the renin-angiotensin-system, is capable of increasing PAI-1 levels in both hypertensive and normotensive patients. Angiotensin converting enzyme (ACE) converts angiotensin I to angiotensin II. The inhibitors of ACE decrease PAI-1 activity in hypertensive patients [72]. ACE inhibitors can cause the elevation of bradykinin, which is a potent stimulator of t-PA. Thus, the inhibitors of ACE and angiotensin II-mediated signaling use provide better BP control and fibrinolytic parameters.

Cardiovascular Risk Factors that raise Vascular Dementia Risk

Diabetes mellitus

Diabetes is characterized by hyperglycemia due to decreased insulin release, sensitivity, or both. Type 1 is due to autoimmune destruction of beta cells, while type 2 is caused by progress loss of insulin secretion from beta cells. An estimated 1 in 10 people currently have diabetes, with 95% of cases being type 2 [73]. The clinical complications of diabetes are vast including cardiovascular disease, retinopathy, nephropathy, and neuropathy [74].

The vascular complications that arise from uncontrolled diabetes include atherosclerosis, retinopathy, and nephropathy. Vasculopathy is associated with elevated cholesterol/triglycerides [75]. Insulin resistance along with overproduction of reactive oxygen species and advanced glycation end products promote endothelial cell dysfunction [76]. Significant vascular remodeling (increased tortuosity collateral numbers and collateral size) can occur as early as 4 weeks after the induction of diabetes (blood glucose levels over 300 mg/dL). A duration of 10-12 weeks has also been associated with increased wall thickness of cerebrovascular arteries in an ET-1 (endothelin-1, a potent vasoconstrictor) dependent manner. Studies have linked decreased vessel density to diabetes as well, however conflicting evidence leaves the effect on microvascular density unclear.

The microvascular diseases accompanied by diabetes have been shown to have a link to cognitive impairment by various studies. The presence of microvascular disease in diabetic patients is associated with a reduced maintenance of cerebral blood flow, with disruption of this blood flow potentially leading to damage and subsequent cognitive impairment. The areas of the brain shown to be most affected through single-photon emission computed tomography (SPECT) were the cerebellum, frontotemporal brain, and frontal brain [77].

One study showed T1D and T2D to be associated with a marked increase in ischemic stroke risk, with relative risk of 1.5-2 fold increase in men and 2-6.5 in women with T2D. Stroke risk in T1D was higher with a 4 fold increase at all ages and 16 fold at ages 15-34 [78]. Diabetes is also linked with worsened stroke outcome. Acute hyperglycemia increases risk of intracerebral hemorrhage following reperfusion therapy, potentially leading to further cognitive impairment or death [79].

All the threats that diabetes poses to the macro-and micro-cerebrovasculature potentially link the disease to an increased risk of ischemic or hemorrhagic brain injury induced cognitive impairment.

Hypertension

The new ACC/AHA guidelines define stage 1 hypertension as an average blood pressure of 130-139/80-89 mmHg and stage 2 as ≥ 140/ ≤ 90. Hypertension typically has no visible symptoms and must be measured to be detected. Nearly half of the adults in the US have hypertension with about a fourth of them not having it controlled, and an estimated 1 in 5 adults with hypertension are unaware of the disease [80]. Uncontrolled hypertension increases risk for heart disease and stroke, and there are many overlaps between diabetes and hypertension in terms of microvascular and macrovascular complications [81].

The vascular complications arising from hypertension include endothelial dysfunction, vascular inflammation, arterial remodeling, and atherosclerosis. Many of these symptoms and their mechanisms go hand in hand with diabetes and contribute to the two chronic diseases being commonly associated with each other [81]. Studies have found an association between random blood pressure variability and cardiac, cerebrovascular, and peripheral vascular events. However, it is unknown if the impact is similar at these different levels, or rather the variance of impact between cardiac, cerebrovascular, and peripheral [82]. Hypertension may also lead to a lowered density in arterioles and capillaries, lowering cerebral blood flow and increasing the risk of cognitive decline in patients. For these reasons hypertension has previously been identified as a major modifiable risk factor of cerebral small vessel disease (sCVD) with high, and low especially in elderly patients, blood pressure being linked to cognitive decline. Despite this, results of studies anti-hypertensive control impact on cognitive function have been inconclusive [83].

Inflammation is a pivotal link between cardiovascular diseases and the activated endothelial cells

Both diabetes and hypertension lead to cerebral microvascular complications through the similar mechanisms of arterial remodeling, inflammation, endothelial dysfunction, and inflammation. These reported factors cannot be used as conclusive evidence to make the claim that diabetes and hypertension cause cognitive decline. However, there are several recorded instances of these microvascular complications, arising from diabetes and hypertension, having a negative effect on the cerebrovasculature. There are also many studies which suggest a strong link between microvascular complications, cerebrovascular complications/ischemic brain injury, and cognitive decline *via* vascular dementia. Therefore, it can be suggested that these two diseases, which patients are often diagnosed with together, work together to cause damage to the cerebrovasculature, lower perfusion of the brain, and lead to neuronal death and further cognitive decline.

Conclusion

With all the links that have been drawn from hypertension and diabetes to ischemic induced vascular dementia more research must be done on the potential benefits of anti-hypertensive and diabetic treatment on cognitive function. By modifying these risk factors cognitive decline may be prevented or even reversed.

Conflicts of Interest

The authors have declared no conflict of interest.

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Authors Contribution Statement

Z.S. designed and wrote the paper. B.H. contributed to the writing of the manuscript.

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