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Review Article

Collagen type IV as the link between arterial stiffness and dementia

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Abstract: Arterial stiffness has been linked to impaired cognitive function and dementia but the reason for the association is uncertain. This review proposes that collagen type IV is a critical factor linking arterial stiffness and dementia. Several genome wide association studies have related arterial stiffness to Collagen type IVα. Proteomic studies of arteries, demonstrated higher levels of collagen IVα1 in persons with high arterial stiffness. Collagen type IV defects are associated genetic causes of dementia as well as dementia of a variety of other causes. There are plausible causal roles for collagen type IV in dementia. Disorders of Collagen type IV can produce (I) fibro-hyalinosis and elastosis of small arterioles leading to cerebral ischemia and infarction; (II) dysfunction of the blood brain barrier leading to cerebral hemorrhage; (III) carotid artery stiffness with increase pulse pressure induces cerebral blood vessel damage leading to cerebral atrophy. The mechanisms by which Collagen type IV can lead to vascular stiffness include its degradation by matrix metalloprotease type 2 that (a) stimulates vascular smooth muscle cells to produce more extracellular matrix or (b) liberates peptides that damage the subendothelial space. Factors, such as TGF-β1, and LDL cholesterol especially oxidized LDL can increase collagen type IV and produce vascular stiffness and dementia. Fibroblast growth factor 23, and abnormal NO signaling have been linked to collagen type IV or increased vascular stiffness and an increased risk of dementia. Recognition of the central role of collagen type IV in arterial stiffness and dementia will inspire new research focused on determining whether its modification can benefit arterial and brain health.

Keywords: Arterial stiffness, dementia, collagen type IV, LDL cholesterol, nitric oxide, TGF-β1, fibroblast growth factors

Introduction

Vascular or arterial stiffening in the larger arteries is a recognized contributor to a number of cardiovascular disorders and predicts cardiovascular morbidity and mortality [1]. Measurement of arterial stiffness has been assessed clinically by the measurement of pulse wave velocity (PWV) between two segments of the arterial tree, such as the carotid-femoral arteries (cfPWV), brachial-femoral (bfPWV), brachial-ankle (baPWV) as well as the assessment of carotid artery distensibility [1, 2]. Although there are overlaps between vascular dementia and Alzheimer's disease, aortic stiffness has been linked to Alzheimer's disease and vascular dementia both of which involves significant impairment in cognitive function leading to dementia [3]. A multivariate analysis within a meta-analysis, after adjusting for a wide range of possible confounding factors, concluded that the majority of studies comprising over 6,000 individuals showed a significant relationship between arterial stiffness and dementia [3]. Since that meta-analysis, additional studies have confirmed the association of arterial stiffness and cognitive impairment and dementia [4-8], although there are some exceptions [9]. The relationship of arterial stiffness to dementia is independent of other factor as demonstrated by the significant association of cfPWV with increased risk of dementia, even after adjusting for education, race, ApoE4 status, diabetes mellitus, hypertension and body mass index [8]. Targeted assessment of carotid artery stiffness, has shown an association with impairment of cognitive performance in individuals with or without type 2 diabetes [10].

The question has been asked; what is (are) the etiologic factor(s) that link(s) arterial stiffness to impaired cognitive function and dementia? This article advances the proposal that collagen IV alpha is a critical factor linking arterial stiffness and dementia.

Collage IV alpha

Type IV collagen is a unique kind of collagen, as it resides almost exclusively in the basement membrane in various tissues including arteries [11, 12]. Collagen type IV consists of 6 distinct alpha chains which combine to form three distinct heterodimers that consist of various combinations of trimeric α-chain associations [13]. The genes COL4A1 and COL4A2 reside on chromosome 13, COLA3-COLA4 on chromosome 6 and COL4A5 and COL4A6 on chromosome X [11]. COL4A1 and COL4A2 encode proteins of respectively 1669 and 1712 amino acids that share 45% identity [14]. The protein heterodimers are assembled in the endoplasmic reticulum, then transported to the Golgi and subsequently have vesicular release from the cell [11, 15, 16]. In the extravascular space, the heterotrimers participate in a macromolecular network with lateral interactions via association of their 7S domains [14]. Type IV collagen functions not only as a scaffold for assembly and mechanical stability but also in cell-cell interaction which encompasses cell adhesion, cell migration, proliferation, survival and differentiation [11, 17]. Importantly, type IV collagen is the binding substrate for a range of cell types, including platelets, integrin and non-integrin receptors [11].

Collagen IV alpha and aortic stiffness

Genetics

A genome wide association study (GWAS) of 4221 individuals in a Sardinia cohort found that a SNP (single nucleotide polymorphism) rs3742207 in the COL4A1 gene was significantly associated with PWV [18]. This finding was replicated both in an independent sample within the SardiNIA cohort, and in a separate population of an Old-Order Amish group [18]. The association of rs3742207 and vascular stiffness was independent of age, sex, blood pressure and serum creatinine [18]. In another cohort - the Twins UK cohort, in a subset of 121 women who had repeat measurements of vascular stiffness (cfPWV and carotid distensibility), COL4A1 gene expression was significantly associated with progression of vascular stiffness over approximately a 4 year time frame [19]. In multivariate regression analysis, the transcripts most strongly correlated with progression of cfPWV were COL4A1 and ENPP1 [19]. COL4A1 expression correlates with long term improvement in aortic stiffness (aortic PWV) after bariatric surgery as COL4A1 expression in white adipose tissue was the only one (out of 52 genes examined) that independently predicted PWV improvement after adjusting for age, sex, blood pressure, heart rate and cigarette smoking status [20]. Indeed, COL4A1 explained 25% of the change in vascular stiffness over time [20]. In a Chinese Uygur population, but not another Chinese group, two SNPs (rs605143 and rs565470) of the COL4A1 gene were significantly associated with PWV and the difference remained significant after multivariate adjustment [21]. In contrast to these studies, the Framingham study did not report an association of arterial stiffness with these SNPs [22], however, the chip used in that study apparently 'did not include rs3742207 or any neighboring SNP in the same linkage disequilibrium' [18]. Although other SNPs in the COL4A1 gene have been associated with PWV after adjustment for age and sex [18, 22], but this was not always consistent [23].

Proteomics

Arterial levels of collagen type IV are associated with vascular stiffness. Protein extracts of the left mammary arteries at the time of cardiac surgery, demonstrated higher levels of collagen IVα1 in persons with high arterial stiffness (cfPWV) [24]. Four hundred and eighteen proteins were examined and 28 proteins were found to be differentially expressed in patients with increased cfPWV [24]. In multivariate analysis including consideration of blood pressure, collagen type IVα-1 was one of only 9 proteins that characterized patients with increased arterial stiffness [24].

Interestingly, peroxidasin knockout mice, with reduced collagen type IV sulfilimine cross-links, manifest a reduction in renal tubular basement membrane stiffness establishing a role for collagen type IV in organ stiffness and linking it to

the sulfilimine cross-links in collagen type IV [25].

Putative mechanisms

There are a number of potential explanations for the relationship between COL4A-1 and vascular stiffness. One proposal has indicated that degradation of collagen type IV by matrix metalloprotease, type 2, a collagenase secreted and activated by vascular smooth muscle cells, permits vascular smooth muscle cells to enter the subendothelial space where they produce more extracellular matrix which in turn stiffens the artery [18]. A similar postulate is that degradation of type IV collagen by matrix metalloproteases liberates peptides that may damage the composition of the subendothelial space [18]. Another mechanism is that COL4A increases intima thickness and by altering endothelial function and thereby increase arterial stiffness [20].

Fibroblast growth factor 23 (FGF23) levels in the population are associated with vascular stiffness independent of age, sex, biochemical covariates and established CV risk factors [26]. The association is especially strong in patients with chronic kidney disease (CKD) [27]. Serum FGF23 levels are significantly increased in mice containing the targeted deletion of the NC1 domain of the Collagen type IVα3 chain [28]. The mechanism by which FGF23 increases vascular stiffness maybe operative through FGF23-induced increases in superoxide that inhibits NO bioavailability, and causes endothelial dysfunction [29]. Ferric citrate, an oral phosphate binder that decreases serum FGF23 concentrations in patients with CKD, reduced renal fibrosis in the Col4a3 knockout rat model of CKD [30]. To the extent that renal fibrosis mirrors the increase in collagen in large vessels, higher circulating levels of FGF23 can induce vascular stiffness. Fibroblast growth factor 21 is association with arterial stiffness in type 2 diabetes mellitus [31]. Advanced glycation end products, common in diabetes mellitus, are linked to arterial stiffness, possibly through binding to the non-collagenous NC1 domain of type IV collagen as well as binding to itself to form dimers and in turn interfere with normal assembly of type IV collagen [32].

COL4A1 mutations lead to defects in the maintenance of vascular tone and endothelial cell function [33]. COL4A1 mutations are associated with reductions in basal nitric oxide synthase activity attributed to defective deposition of collagen type IV in the basement membrane, that activates an unfolded protein response [33].

An Ingenuity Pathway Analysis found that COL4A1 mutations, associated with worsening PWV, are regulated by the CTNNB1 gene which produces β-catenin that regulates and coordinates cell-cell adhesion and gene transcription [19]. Interestingly, β-catenin signaling may be associated with increased cyclin D1 expression and VSMC proliferation and may play an role in vascular disease [34].

Collagen IV alpha and dementia

Genetic mutations in collagen type IV alpha chains (COL4A1 and COL4A2) have been associated with a spectrum of cerebrovascular, renal, ophthalmological, cardiac, and muscular abnormalities [35]. The phenotypic manifestations, however, are quite variable [35]. COL4A1 upregulation has been proposed to be a central factor in the pathogenic mechanism producing both Swedish hereditary multi-infarct dementia (hMID) and pontine autosomal dominant microangiopathy and leukoencephalopathy (PADMAL) [36-38]. Both of these genetic variants are associated with fibro-hyalinosis and elastosis of small arterioles with atrophy of media and proliferation of the intima, all of which can lead to multiple lacunar infarcts and white matter atrophy presumably through reduction in cerebral blood flow [38]. Although there are no precise data, it has been suggested that mutations in COL41/2 account for a large proportion of familial cases of small vessel disease [39].

Another type of dementia - Lewy body dementia is associated with insoluble aggregates composed mainly of phosphorylated alpha-synuclein (αSyn) [40]. In A30P alpha-synuclein transgenic mice, COL4A2, was upregulated in the brain implicating this collagen in αSyn-induced toxicity [41]. αSyn can elicit an ER stress response, sensitize cells to further insult and promote the aggregation of wild type αSyn [42].

Independent of the presence of genetic abnormalities of COL4A1/2, brains of patients with dementia of different causes, show microinfarcts and a dense microvascular meshwork of

collagen type IV-positive micro-vessels with numerous string vessels [43]. Collagen type IV-positive string vessels have been suggested to represent endothelial recession, which is associated with cessation of blood perfusion in the vessels affected [43, 44].

Mechanism of collagen type IV and dementia

There are a number of potential mechanisms whereby collagen type IV can play a causative role leading to dementia. Animal models suggest a direct relationship between increased carotid arterial stiffness and reduced cerebral blood flow leading to cognitive dysfunction in mice [45]. Carotid arterial stiffness, in mice, is associated with increased collagen type IV in cerebral vessels in the somatosensory cortex [45]. Abnormalities of collagen type IV can produce narrowing in cerebral small arteries producing insufficient blood flow due to small vessel disease [39] which leads to microinfarcts and brain atrophy, resulting in cognitive dysfunction and dementia [46, 47]. Another mechanism involves the key role that collagen type IV plays at the basement membrane which forms the blood brain barrier which is composed mainly of endothelial cells, pericytes, astrocytes and the basement membrane [48]. The basement membrane contributes critically to the functioning of the blood brain barrier [49]. Damage or dysfunction of the blood brain barrier has been implicated in the pathogenesis of vascular cognitive impairment [50]. Impairment in cognitive function on a vascular basis, as well as vascular dementia, have been attributed, in part, to damage to the blood brain barrier producing cerebral micro-hemorrhages [51]. Thus, alterations of the blood brain barrier by defects or alteration of collagen IV can reasonably be linked to loss of cognitive function. This is consistent with the increasing data linking the extracellular matrix of the blood brain barrier with neurodegenerative diseases [52].

NO induces the expression of integrin $\alpha_v\beta_3$ in endothelial cells which play a role in facilitating endothelial cell adhesion to the basement membrane matrix [53]. NO-induced increases in collagen type IV synthesis, in pulmonary endothelial cells act via a PKG signaling pathway and then through an integrin-FAK signaling pathway [54]. There is a feedback mechanism as inhibition of collagen type IV synthesis decreases FAK phosphorylation and inhibits NO-induced increase in FAK phosphorylation [54].

Possible dysregulation of collagen type IV biosynthesis leading to arterial stiffness and/or vascular dementia

The biosynthesis of collagen type IV is complex and involves many posttranslational modifications catalyzed by several specific and nonspecific enzymes and other factors [11, 55]. Factors that increase biosynthesis of collagen type IV include: high shear stress that increases type IV collagen mRNA in endothelial cells [57], TGF-β1 that stimulates expression of collagen type IV mRNA [58-61]. TGF-β1 expression is increased by high glucose, angiotensin II, reactive oxygen species, lipids, and thromboxane A2 [59]. Autocrine production of TGF increases collagen IV production [60], high glucose, independent of TGF-β1 [61] increases secretion of collagen type IV. LDL, independent of TGF-β1, increase expression of collagen IV in endothelial cells via activation of the MAPK pathway [74], LDL-C and oxidized LDL can operate through immune complexes engaging Fc gamma receptor I and III with the involvement of p38 MAPK, JNK and PKC pathways producing an increase in collagen IV expression [80].

Generally, collagen synthesis has been considered to involve three collagen hydroxylases, two collagen glycosyltransferases, two specific proteinases to cleave the N and C propeptides from the procollagen molecules and one specific oxidase to initiate crosslink formation [55]. Other enzymes include peptidyl proline *cis-trans* isomerase and protein disulfide isomerase, as well as the chaperone Hsp47, which perform various functions in collagen formation [55]. Some investigators contend that the normal expression of collagen type IV is under controlling mechanisms specific to each organ and to individual chains [56].

Patients with repaired coarctation of the aorta have increased vascular stiffness and this impairment in arterial elasticity is strongly associated with elevations in plasma TGF-β levels compared to healthy age- and sex-matched control subjects [62]. Animal models support the relationship between TGF-β and vascular stiffness. Decreased miR-181b with aging plays a critical role in extracellular matrix remodeling

by removing the brake on the TGF-β, pSMAD2/3 pathway [63]. In a mouse model of Western diet (high-fat/high-sugar), TGF-β signaling is a contributor to femoral artery stiffening [64]. TGF-β was also increased in aorta tissue of mice on a high fat diet that was associated with the increase in aortic stiffening [65].

Overexpression of TGF-β1 has been found in the brain in Alzheimer dementia and is associated with neuro-inflammation, accumulation of extracellular matrix compounds, cerebrovascular stiffness, and the development of vascular hypertrophy [66]. Transgenic mice overexpressing TGF-β1 have similar lesions in the brain as Alzheimer disease-like cerebrovascular pathology [66].

TGF-β1-induced anti-apoptotic factor leads to dephosphorylation of amyloid precursor protein at Thr668, followed by its degradation leading to amyloid fibrils [67]. Genetic studies also support a role for TGF-β1 in Alzheimer-dementia [68].

Fibroblast growth factor (FGF) is associated with arterial stiffness in several but not all studies [27, 31, 69, 70]. Higher circulating FGF23 was associated with an increased risk of dementia, in the Framingham study, suggesting that FGF23-related biological pathways may play a role in the development of dementia [71]. Acidic FGF potentiates glial-mediated neurotoxicity by activating FGFR2 IIIb protein [72] and brain neuronal loss leads to impairment in cognitive function.

Increased low density lipoprotein cholesterol (LDL-C) can link collagen type IV to dementia. Hypercholesterolemia increases collagen type IV expression and produces fibrosis [73]. LDL-C exerts a significant effect on the expression of collagen type IV [74]. LDL-C is associated with an increased risk of Alzheimer disease, independent of other vascular risk factors even after adjustment for APOE-4 carrier status [75]. Elevated LDL-C levels were associated with higher probability of having early onset Alzheimer disease [76]. Two meta-analysis have demonstrated that LDL-C levels is a risk factor for cognitive impairment [77, 78]. While LDL-C increases collagen IV expression, oxidized LDL-containing immune complexes oxLDL-markedly stimulated collagen type IV expression [74, 79, 80]. LDL exerts a significant effect on the expression of collagen IV in endothelial cells via activation of the MAPK pathway [74]. LDL enhances connective tissue growth factor (CTGF) promoter activity, the mRNA and the protein levels of CTGF, TGF-β, and collagen type IV in endothelial cells [74]. LDL-C can be operative through TGF-β, and in addition oxidized LDL containing immune complexes engages Fc gamma receptor I and III with the involvement of p38 MAPK, JNK and PKC pathways to increase collagen IV expression [80].

Several factors can operate in both pathways to produce vascular stiffness and cognitive impairment. LDL cholesterol is associated with the development of arterial stiffness [81, 82] and LDL cholesterol lowering therapy mainly with statins reduces arterial stiffness [83]. Nitric oxide may play a role in linking vascular stiffness and dementia. Endothelial function and NO bioavailability are important determinants of aortic biomechanics and function [84], suggesting that impaired NO availability would increase vascular stiffness. This proposal is supported by the study that increasing NO availability by dietary supplementation of its precursor L-citrulline can reduce a person's arterial stiffness [85]. Reduced nitric oxide bioavailability by endothelial NOS (nitric oxide synthase) can reduce cerebral blood flow [86]. Alzheimer disease may compound the problem as amyloid-beta peptides can generate reactive oxygen species that increase NO degradation [87]. Abnormal NO signaling has been linked to various neurodegenerative diseases including Alzheimer's disease [88].

In summary, there are a number of specific factors that are associated with increased vascular stiffness and include: TGF-β [62], fibroblast growth factor (FGF) [27, 31, 69, 70], FGF-23 [27, 70], LDL cholesterol [81-83] and impaired NO availability [85]. There are a number of vascular factors that are associated with impaired cognitive function and/or dementia, and include: TGF-β which is associated with Alzheimer dementia [66-68], FGF23 which is not only associated with an increased risk of dementia [71] but also is associated with axonal loss in the frontal lobe and fragmentation of white matter network organization [90]; acidic FGF potentiates glial-mediated neurotoxicity by activating FGFR2 IIIb protein and brain neuronal loss that leads to impairment in cognitive

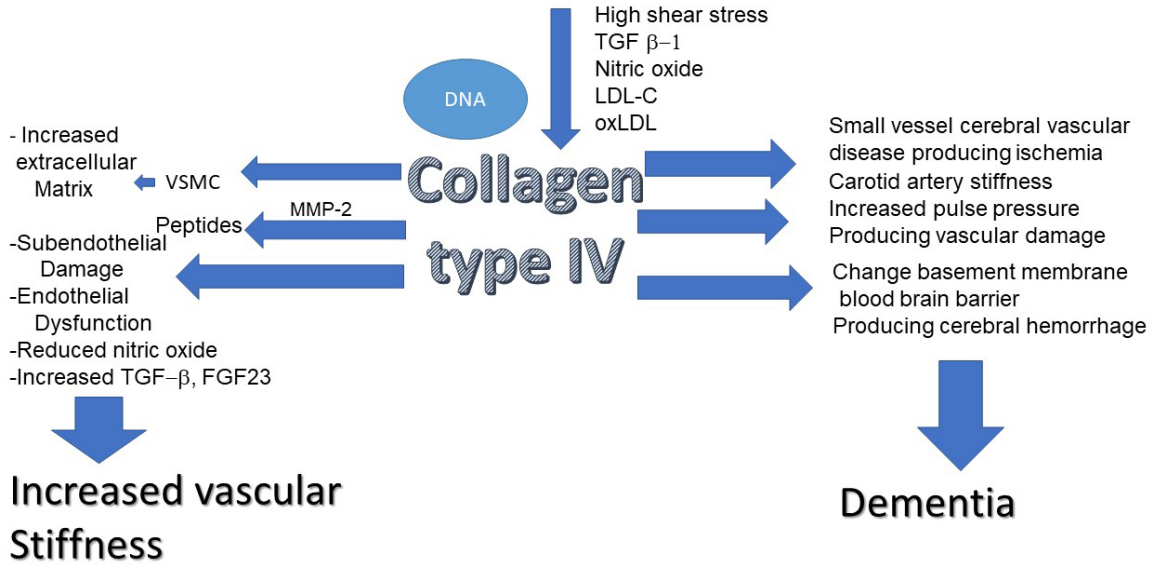

Figure 1. A summary schema of the central role of Collagen type IV and vascular stiffness or Dementia.

function [72]. LDL-C that is associated with an increased risk of Alzheimer disease, independent of other vascular risk factors even after adjustment for APOE-4 carrier status [75]. Abnormal NO signaling that has been linked to various neurodegenerative diseases including Alzheimer's disease [88].

Conclusion

There is ample evidence to link Collagen type IV in the pathogenesis of both vascular stiffness and dementia through a number of different pathways (**Figure 1**). It is unlikely that collagen type IV is the only factor explaining the relationship between arterial stiffness and the cognitive decline, in patients with vascular stiffness. Arterial stiffness itself may compromise cerebral blood flow leading to neurodegeneration and cognitive impairments [45], or a systemic increase in pulse pressure produced by increased arterial stiffness may lead to structural damage to cerebral small vessels [89]. However, available data on COL4A1 mutations, and factors modulating collagen type IV synthesis and degradation, link collagen type IV to both vascular stiffness and dementia. These data suggest next steps to test the common mechanism(s) to determine whether specific therapies will benefit arterial and brain health.

Disclosure of conflict of interest

None.

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