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Review Article

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COMPARISON OF EFFECT OF DIABETIC MELITUS, HYPRTENSION AND DISLIPIDEMIA ON COGNITIVE FUNCTION-A SYSTEMIC REVIEW

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ABSTRACT

Vascular risk factors such as type 2 diabetic mellitus, hypertension and dyslipidemia have been associated with an increased risk of cognitive dysfunction, particularly in the elderly. The aim of this review was to compare the risk factors with regarding cognitive decrements. Cross sectional study and longitudinal studies assessed cognitive functioning in person related to diabetes, hypertension and dyslipidemia and that adjusted or matched for age, gender and education were included. Diabetes and hypertension were clearly associated with cognitive decrements, the results for dyslipidemia were less consistent.

INTRODUCTION

Cognitive impairment is when a person has trouble recollecting, understanding new things, attention, or making decision that affects their everyday life. There are two types of cognitive impairment: mild cognitive impairments and severe cognitive impairments. Mild cognitive impairment is a brain function syndrome involving the onset and evolution of cognitive impairments beyond those expected based on the age and education of the individual, but which are not significant enough to interfere with their daily activities.[1] Losing the ability to walk or write, resulting in the inability to live independently may be due to the severe levels of impairments. Although age play an important role in cognitive impairments and dementia it is increasingly recognized that the case of dementia and cognitive impairment may be attributable to vascular risk factors like diabetic mellitus, hypertension, and dyslipidemia.[2,3] Life style factors like smoking, lack of physical exercise, low education level and infrequent participation in mentally or socially stimulating activities also linked to the increased risk of cognitive change. Metabolic abnormalities, including abdominal obesity, elevated blood pressure (BP), elevated blood glucose levels, low high density lipoprotein cholesterol levels, and elevated triglyceride (TG) levels also play a major role in the development of cardiovascular disease.[4]

MATERIALS AND METHOD

The systemic review aimed to include all published studies that examined the association between cognitive function and conditions like diabetic mellitus, hypertension, and dyslipidemia or obesity and that met the following criteria: the studies

(1) That published after 2000,
(2) Had a population- based or case control design
(3) Matched or adjusted the exposed and the non-exposed groups for the basic confounder's age, sex, and education level.

1. Cognitive Function and Diabetic Melitus

Dementia and diabetes are two prevalent conditions affecting older people. Diabetic patients are at high risk for vascular damages leading to neuropathy, nephropathy, retinopathy, and cardiovascular and cerebrovascular diseases.[5] Previous studies suggest that cognitive impairment is another complication in elderly patients with diabetic mellitus. In diabetic patients the risk factors for dementia and cognitive impairment are duration of disease, hyperglycemia, insulin therapy, and peripheral arterial disease. Complications like retinopathy, nephropathy, and neuropathy and diabetes related disorders including Ischemic heart disease, cerebrovascular disease, hypertension, low serum HDL, and obesity also are a reason cognitive dysfunction.[6]

Insulin therapy and cognitive dysfunction

A common pathologic feature of the metabolic syndrome is insulin resistance (IR) which involves a progressive reduction in the responsiveness of peripheral tissue to insulin systemic IR and defective brain insulin signaling are common features of Alzheimer's disease. Insulin alters normal brain function and peripheral glucose metabolism while conditions related to insulin disintegration such as obesity, diabetes mellitus and

cardiovascular disease have potentially harmful effects on brain function. Insulin modulate catecholamine release and uptake, regulate ligand gated ion channels modulate activity depend synaptic plasticity and play important role maintenance of excitatory synapses.[7]

Table 1: Description of included studies for type 2 DM.

Cross- sectional	Design	N	Age	Exclusion criteria	Conclusion
Elias et al.[8]	P	1811	68	Stroke DM1	Hypertensive DM2 patients were at greatest risk of cognitive impairment (<25%)
kilander et al.[9]	P	504	72	Not specified	DM2 was associated with a significantly lower composite z score
Scott et al.[10]	P	1131	74	Not specified	No association between DM2 and cognitive functioning
Grodstein et al.[11]	P	2374	74	VD	DM2 was associated with a significantly lower composite z- score
Longitudinal					
Kumari et al.[12]	P	5647	-45	Not specified	Baseline DM2 was associated with worse cognitive performance after 12 years
Knopman et al.[13]	P	10963	47-70	Stroke	DM was associated with greater decline over 6 years
Fontbonne et al.[14]	P	926	40	MMSE <27	DM2 patients had a 1.5 to 2 fold increased risk of serious worsening over 4 years
Van den Berg et al.[15]	P	664	85	Not specified	DM2 patients was associated with worse attention and speed at baseline, but not with accelerated decline over 5 years

P- population-based design.
All studies were age, sex and education-adjusted or -matched, additional adjustments are listed.

2. Cognitive Function And Hypertension

High blood pressure represents a key factor in development of cerebrovascular diseases. Cognitive impairment also arises in the early stages of hypertension. There are important evidences that results of cognitive tests in predicting hypertensive target end organ damage. Cognitive impairment is mainly due to the age and structural changes in cerebrovascular blood vessels. In hypertensive patients, so many changes occur such as.[16,17]

- Reduced cerebral mantle capillaries with thickening
- Formation of fibrotic basement membrane
- Changes in white matter

This may reduce cerebral blood flow and dysfunction of cerebral regulatory mechanism. Subsequently, imbalance in auto regulation of cerebral blood flow and cerebral vascular alteration causes the hypertensive cognitive impairments.18]

Arterial stiffness is another cause of hypertensive cognitive impairments.[19] Cooper et al reported that relationship between aortic stiffness and cognitive function in older is the consequence of damage in cerebral microvascularisation and microvascular parenchymal injury.[20] In elderly patients white matter reduced due to the cerebral small vessel disease increased pulse pressure and arterial stiffness white matter particularly found in frontal lobe.[21,22] The other causes of hypertensive cognitive impairment are.

- Activation of renin-angiotensin-aldosterone system and oxidative stress
- Endothelium mediated constriction and brain damage
- Alteration in vasodilator mechanism
- Blood brain barrier damage through direct effect of an oxidative stress inflammation and vasoactive substances.
- Cytotoxic substance leading to neuronal loss

Individuals exposed to hypertension for many years, especially high systolic blood pressure present greater brain atrophy in relation to controls without hypertension on magnetic resonance imaging independently of the occurrence of stroke. The exposition to hypertension throughout life causes vascular hypertrophy and vascular remodeling, promoting atherosclerosis in large vessels and lipohyalinosis in penetrating arteries.[23]

Hypertension is an independent risk factor for the occurrence of white abnormalities, with stronger correlation associated with time. Some studies report that circadian variations of BP are associated with higher incidence of white matter abnormalities on structural neuroimaging. The hypo perfusion affected mainly the cingulate gyrus, the occipital and prefrontal cortices. In the hippocampal region controls presented a relative increase in blood flow on follow- up, probably caused by decreased flow in other areas.

The reduction in the cerebral blood flow leads to an increase in the expression of the beta-amyloid precursor protein causing a rise in the production of beta-amyloid pepetide. This reduced flow also causes a dysfunction in

the blood-brain barrier leading to an increase in the expression of beta-amyloid peptide as well as apolipoprotein E. these neurological changes are classic hallmarks of the pathophysiology of Alzheimer's disease.[24]

Table 2: Description of included studies in hypertension.

	Design	N	Age	Exclusion criteria	Conclusion
Cross sectional					
Van Box et al.[25]	P	936	24-80	Stroke, dementia,N/P comorbidity,	Hypertensive participants only showed significantly worse performance on measure of cognitive speed
Cerhan et al.[26]	P	13840	45-64	Stroke,N/P comorbidity, old age	Differences were statistically significant for women only
Desmond et al.[27]	P	249	71	Stroke	No relation between blood pressure and cognitive function
Morris et al.[28]	P	5816	>65	Not specified	Modest inverted U-shape relation between blood pressure and cognitive function
Longitudinal					
Pavlik et al.[28]	P	3270	30-59	Stroke, N/P comorbidity	Hypertension was associated with cognitive function when combined with DM2
Swan et al.[30]	P	717	39-59	Not specified	Persistent elevated SPB and SPB decrease over 38years follow up was associated with worse cognition
Swan et al.[31]	P	392	47	Vascular dementia	High midlife SPB was associated with greater 10-year decline in cognitive speed
Wolf et al.[32]	P	1814	53	Stroke, dementia	Hypertension was associated with worse cognitive performance particularly in obese individuals

P-population-based design.
N/P comorbidity-neurological or psychiatric comorbidity (including epilepsy, Parkinson's disease, malignancies in central nervous system, sensory of motor neuron disease, depression, psychoactive medication such as sedatives, anticonvulsants, substance abuse, mental retardation, head trauma).
All studies were age, sex and education-adjusted or -matched, additional adjustments are listed.

3. Dyslipidemia And Cognitive Function

One of the modifiable risk factor for cognitive impairment is serum lipoprotein level. Aging and dementia, midlife measures of total cholesterol were significant predictors of cognitive impairment. Moreover; it was shown that a high midlife cholesterol level increased the risk for VaD. Some studies have reported that higher levels of late-life cholesterol were associated with a higher risk of VaD

Mechanism of influence of plasma lipids on cognitive function.

- **Blood Brain Barrier**

Brain cholesterol is involved in synapse development, synapse formation, dendrite differentiation, axonal elongation, and long term potentiation.[33] Plasma cholesterol/lipoprotein compartments are strictly segregated by the blood-brain barrier (BBB). The BBB is created by the tight junctions between the endothelial cells of brain microvascular tissue and the astrocyte foot processes surrounding capillary endothelial cells. BBB injury has been recognized as a contributory factor to the development and progression of cognitive impairment. Recently, multiple studies have reported that rats fed with high energy diets, specifically diet rich in saturated fats and cholesterol, exhibited increased BBB permeability along with cognitive dysfunction.[34,35] A recent study showed that the activation of microvascular endothelial cells by LDL increased the secretion of the inflammatory mediators such as tumor necrosis factor alpha and interleukin-6 and decreased the membrane localization of the tight junction protein. In conjunction with these studies, another investigation demonstrated that anti-inflammatory and lipid-lowering agents could reverse the high fat-induced BBB damage in rats. HDL-C might be involved in the removal of excess cholesterol from the brain mediated by ApoE and heparin sulfate proteoglycans in the sub endothelial space of cerebral micro vessels. HDL particles also reverse the inhibitory effect of oxLDL particles.[36]

- **Influence Of Small Blood Vessels In The Brain**

One cohort study (n = 1919) revealed a significant relationship among increased HDL-C, decreased LDL-C, and white matter hyperintensity (WMH) progression.[37] Furthermore, in 1135 acute ischemic stroke patients, hypercholesterolemia, hypertriglyceridemia, or the use of lipid-lowering medication was associated with a decreased severity of WMH.[38]

- **Influence On The Deposition Of Amyloid**

Some evidences indicate that changes in brain cholesterol homeostasis are associated with the main pathological features of AD, especially amyloid beta (Aβ). Evidences also suggest that amyloidogenic

amyloid precursor protein (APP) processing might preferentially occur in the cholesterol-rich regions of membranes known as lipid rafts and that alterations in cholesterol levels could exert their effects by altering the distribution of APP-cleaving enzymes within the membrane.[39]

- **Neuroprotective Effect**

Some in vitro studies have shown that cholesterol acts as an antioxidant and therefore plays a protective role in dementia pathogenesis, they act through prooxidants to create oxysterols, which are less toxic than free radicals.[40] High cholesterol act as protective effect by increasing gamma-glutamyltransferase which is the enzyme plays an important role in amino acid uptake and transport and reduce the neurotoxic effects of amino acids.[41]

Table 3: description of included studies in dyslipidemia.

	Design	N	Age	Exclusion criteria	Conclusion
Cross sectional					
Zhang et al.[42]	P	4110	37	Stroke	Low total and non HDL cholesterol associated with decreased cognitive speed in men
Dik et al.[43]	P	1183	75	>65 years	Low HDL cholesterol but not high triglycerides was associated with worse speed and fluid intelligence
Longitudinal					
Henderson et al.[44]	P	438	49	Not specified	Highest quartile of LDL and increase in LDL and total cholesterol over 8 years associated with better memory performance
Komulainen et al.[45]	P	101	64	Not specified	Low HDL cholesterol was associated with increased risk of poor memory after 12 years follow up
Reitz et al.[46]	P	1147	76	Stroke, dementia, N/P comorbidity	Lipid levels were not associated with 7 year changes in cognitive function.

P-population-based design

N/P comorbidity-neurological or psychiatric comorbidity (including epilepsy, Parkinson's disease, malignancies in central nervous system, sensory of motor neuron disease, depression, psychoactive medication such as sedatives, anticonvulsants, substance abuse, mental retardation, head trauma).

All studies were age, sex and education-adjusted or -matched, additional adjustments are listed.

DISCUSSION

In this review the association between type 2 diabetes, dyslipidemia, and hypertension and cognitive functioning was examined. Eight studies compared cognitive functioning in patients with type 2 diabetes mellitus to non-diabetic persons (Table 1). Half of the population studies were cross-sectional studies and another half is longitudinal studies, seven of the studies commented that there is relation between type 2 diabetic mellitus and cognitive decline one study did not find any relation between diabetic mellitus and cognitive decline (Scott et al). For find outing the relation between hypertension and diabetic mellitus nine studies are included and four of the study are cross sectional and five of the study is longitudinal and seven of the studies observed worsening of cognitive speed with respect to hypertension.in case of dyslipidemia and diabetic mellitus five population studies are examined two cross-sectional studies and five longitudinal studies but the results were varying for each studies cognitive speed varies according to different levels of lipid proteins thus studies did not show an association with worse cognitive performance. Even though some studies found that low HDL level will be risk factor for the cognitive decline.

CONCLUSION

Comparison of the results over the four vascular factors shows that most consistent associations with cognitive decline are found for diabetes and hypertension, results for dyslipidemia are less consistent thus more study is required in this area.

Abbreviations

BP-Blood Pressure
TG-Triglycerides
LDL-Law density Lipoprotein
HDL/HDL-C –High Density Lipoprotein Cholesterol
IR- Insulin resistance
DM- Diabetic Mellitus
VD/VaD – Vascular Dementia
MMSE- Mini Mental state examination
BBB- Blood Brain Barrier
oxLDL- oxidized law density lipoprotein
WMH- White matter hyperintensity
AD- Alzheimer's disease
APP- Amyloid precursor protein

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