Metabolic Syndrome and Alzheimer's Disease: *A Link to a Vascular Hypothesis?*

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ABSTRACT

Current evidence from epidemiological, neuroimaging, pathological, pharmacotherapeutic, and clinical studies indicate an association of Alzheimer's disease with risk factors of vascular atherosclerotic disease either in isolation or in aggregate. "Metabolic syndrome" (MetS) is the name for a clustering of risk factors for cardiovascular disease and type 2 diabetes that are of metabolic origin. These include central obesity, elevated plasma glucose, high blood pressure, atherogenic dyslipidemia, a prothrombotic state, and a proinflammatory state. In this article, we provide an overview of the relevant literature with regard to the relationship of Alzheimer's disease with MetS. Accumulating evidence suggests a "vascular hypothesis" to be related to the pathology of Alzheimer's disease. In the light of this evidence, clinician may consider lifestyle interventions toward an early and effective cardiovascular risk-factor management to reduce the cardiometabolic and the cognitive decline risk, while further research of other preventive strategies may be warranted.

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Needs Assessment

Current evidence suggests an association between Alzheimer's disease and vascular risk factors. Metabolic syndrome represents a constellation of risk factors for cardiovascular disease and diabetes. There is increasing evidence indicating a potential relationship between metabolic syndrome and Alzheimer's disease.

Learning Objectives

At the end of this activity, the participant should be able to:
- Understand the diagnostic criteria for metabolic syndrome.
- Discuss the epidemiologic and clinical data indicating the connection between metabolic syndrome and Alzheimer's disease.
- Understand the pathogenesis of Alzheimer's disease.
- Understand the pathophysiological basis of a vascular hypothesis for Alzheimer's disease.

Target Audience: Neurologists and psychiatrists

CME Accreditation Statement

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This activity has been peer-reviewed and approved by Eric Hollander, MD, chair at the Mount Sinai School of Medicine. Review date: June 11, 2008. Dr. Hollander does not have an affiliation with or financial interest in any organization that might pose a conflict of interest.

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INTRODUCTION

Dementia affects almost 7% of all individuals >65 years of age and 30% of people >80 years of age.[1] Alzheimer's disease accounts for >50% of all cases of dementia, vascular dementia follows, representing 15% to 20%, while evidence of both conditions may co-exist in subjects with cognitive decline.[1] The prevalence of dementia from all causes is expected to double in the next 30 years, whereas Alzheimer's disease prevalence is estimated to triple over the next 50 years, making cognitive impairment a serious epidemic that requires therapeutic intervention.[2]

The most popular, widely accepted theory in the pathogenesis of Alzheimer's disease is the "amyloid hypothesis", which relates amyloid-β (Aβ) deposition and formation of senile plaques in the brain.[3] However, there is evidence that supports cerebrovascular pathology as a cause of Alzheimer's disease. There is a number of established cardiovascular risk factors, such as hypertension, atherogenic dyslipidemia, diabetes, and obesity, that cluster to comprise an entity named "metabolic syndrome" (MetS),[4] which is defined by the presence of ≥3 of the following characteristics: a waist circumference >102 cm for men or >88 cm for women, a serum triglyceride concentration >150 mg/dL (1.7 mmol/L), a serum high-density lipoprotein (HDL) cholesterol concentration <40 mg/dL (1.03 mmol/L) in men or <50 mg/dL (1.29 mmol/L) in women, blood pressure levels >130/85 mmHg, and a fasting plasma glucose >110 mg/dL(6.1 mmol/L) (Table 1). Each one of MetS components and MetS itself have been associated with Alzheimer's disease.[5,6]

We overview the relationship between MetS and Alzheimer's disease on a basis of epidemiological, pathophysiological, and clinical evidence.

ALZHEIMER'S DISEASE AND VASCULAR DEMENTIA: ARE THEY REALLY DIFFERENT?

Alzheimer's disease is characterized by gradual onset and continuing cognitive decline, with cognitive deficits not attributed to other central nervous system or medical conditions, whereas vascular dementia is accompanied by evidence of cerebrovascular disease (CVD) that is considered etiologically related to the dementia. However, these clinical entities seem to share most of the risk commonly factors described in subjects with the MetS,[7,8] including hypertension,[9] hyperlipidemia,[9] diabetes mellitus,[10] smoking,[11] obesity,[12] and hyperhomocysteinemia.[8] MetS increases the risk of future diabetes and CVD,[13] conditions closely associated with vascular dementia and Alzheimer's disease.[14]

There is ample evidence indicating an interaction between Alzheimer's disease and CVD. It has been suggested that for a given level of Alzheimer's disease in the brain, the greater is the number of cerebrovascular lesions and the likelihood of clinically significant cognitive impairment/dementia.[15] Furthermore, "silent" strokes,[16] and subcortical ischemic lesions ("white matter lesions")[17] have been linked to cognitive decline and dementia. The most probable underlying mechanism is cerebral hypoperfusion[18] due to atherosclerosis as the underlying pathophysiologic mechanism.

Alzheimer's disease can be distinguished either as an autosomal dominant form (early-onset disease) or as a late-onset disease, the latter accounting for 90% to 95% of all cases.[19] The inherited forms (presenile forms) have been associated with specific mutations of several genes encoding the amyloid precursor protein or proteolytic enzymes, which cleave amyloid precursor protein (eg, presenilin 1 and 2). However, the majority of Alzheimer's disease cases fall into the late-onset disease category, within which heterogeneity also exists, with regard to risk factors, pathogenetic and neuropathological findings. The arbitrary amyloid hypothesis has been disputed by several researchers who suggest a causal relationship between Alzheimer's disease and vascular disease. However, to date, no unanimous theory that explains in detail this association has been established.

Casserly and Topol[7] suggested that vascular risk factors converge to increase the presence of misfolded Aβ, after a substantial incubation period, eventually causing Alzheimer's disease. Roman and Royall[20] regarded ischemic lesions as the main contributor to late-onset dementia clinically diagnosed as Alzheimer's disease, based on data demonstrating a large load of vascular lesions (white matter incomplete ischemia, microinfarcts and large strokes) in elderly demented patients. Kovari and colleagues[21] showed that cortical microinfarcts and white matter lesions explained 30% of the variance in cognition in the elderly. Furthermore, evidence from epidemiological studies[22] support the idea that several ischemic lesions (subcortical lacunes and microvascular lesions) are responsible for cognitive decline. It is most likely that vascular disease co-exists with the amyloid deposition.

COMPONENTS OF METABOLIC SYNDROME AND RISK OF ALZHEIMER'S DISEASE

Epidemiological and Clinical Data

The metabolic syndrome was first described by Reaven[23] as "syndrome X" launching insulin resistance as the primary pathophysiological mechanism of MetS. The current perception is that insulin resistance and subsequent hyperinsulinemia, originating from abdominal obesity, lead to a number of disturbances, all associated with increased risk of coronary heart disease (CHD). The prevalence of MetS depends on the studied population and the definition used (Table 1), but in any case in Western populations more than 20% of adults is affected.[24]

Several large clinical trials have linked MetS and its individual components to increased CVD, CHD, and all-cause mortality.[25] The higher the number of MetS criteria, the higher is the mortality from CVD or CHD.[24] Obesity has been suggested as a risk factor for Alzheimer's disease and vascular dementia[12] and has been associated with poorer cognitive function in population-based investigations.[26] Moreover, the combination of obesity and hypertension has led to diminished performance across various cognitive domains.[27] Hypertension itself has also been associated with cognitive decline[28] as well as with stroke and dementia.[29] In addition, treatment of hypertension protects against dementia, especially in the elderly.[30] Hyperlipidemia has been found, although not in all studies,[31] to increase the risk of dementia.[29] Elevated HDL-cholesterol levels have been associated with a significantly decreased risk of dementia, independent of apolipoprotein E status and other potential confounding variable.[32] HDL cholesterol is the main transporter of cholesterol in the brain, thus, a low HDL cholesterol concentration could result in defective cholesterol release to neurons and subsequent formation of neurofibrillary tangles and senile plaques.[33] There is also evidence of an association between triglyceride levels and an increase in the risk of dementia.[22] Diabetes comprises a strong risk factor for cognitive decline,[34] dementia[29] and Alzheimer's disease.[35] It is of great interest that impaired fasting glucose and abnormal glucose tolerance have also been associated with impaired cognitive performance and greater risk of developing cognitive impairment.[34] Insulin resistance and subsequent hyperinsulinaemia have been found to increase the risk of Alzheimer's disease and promote decline in memory and cognitive dysfunction.[36,37] Furthermore, glycosylated haemoglobin levels have been negatively correlated with cognitive performance.[38]

TABLE 1.
Current Definitions of Metabolic Syndrome

	NCEP ATP III (2001)[4]	NHLBI/AHA (2005)[13]	IDF (2005)[39]
	≥3 of the following	*≥3 of the following*	*The first plus any two of the following*
Central obesity			
Waist circumference			
Men	>102 cm	>102 cm*	≥94 cm*
Women	>88 cm	>88 cm*	≥80 cm*
Hypertension	BP ≥135/85 mmHg	BP ≥35/85 mmHg or specific medication	BP ≥135/85 mmHg or specific medication
Triglycerides	≥150 mg/dL (1.7 mmol/L)	≥150 mg/dL (1.7 mmol/L) or specific medication	≥150 mg/dL (1.7 mmol/L) or specific medication
HDL			
Men	<40 mg/dL (1.03 mmol/L)	<40 mg/dL (1.03 mmol/L)	<40 mg/dL (1.03 mmol/L)
Women	<50 mg/dL (1.29 mmol/L)	<50 mg/dL (1.29 mmol/L) or specific medication	<50 mg/dL (1.29 mmol/L) or specific medication
Fasting plasma glucose	≥110 mg/dL (6.1 mmol/L)	≥100 mg/dL (5.6 mmol/L)	≥100 mg/dL (5.6 mmol/L)

* For subjects of European origin.

NCEP ATP=National Cholesterol Education Program Adult Treatment Panel; NHLBI/AHA=National Heart, Lung and Blood Institute/American Heart Association; IDF=International Diabetes Federation; BP=blood pressure; HDL=high-density lipoprotein cholesterol.

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Although most trials connecting MetS components and other cardiovascular risk factors with dementia included elderly participants, there is an interesting retrospective study which demonstrated an increased risk of late-life dementia in people with multiple midlife cardiovascular risk factors (specifically diabetes, smoking, hypertension and high cholesterol) in a dose dependent manner.[29] These imply a long exposure to the aforementioned risk factors consequently leading to dementia in late life and underline the need for an early preventive strategy against the development of Alzheimer's disease.

Pathogenetic Associations Between Metabolic Syndrome Features and Alzheimer's disease

Central obesity-induced hormonal abnormalities have been related with cognitive decline. Obesity leads to hypercortisolemia,[40] which has been linked to hippocampal atrophy and impaired learning and memory function,[41] as well as to low levels of growth and sex steroid hormones.[40] Obesity-induced hyperleptinemia also seems to contribute to cognitive dysfunction.[42] These neuroendocrine disturbances have been associated with increased sympathetic nervous system activity,[40] which may cause structural brain abnormalities.[43] Finally, inflammation due to central and/or total obesity, as assessed with enhanced proinflammatory markers, such as C-reactive protein, interleukin-6, and tumor necrosis factor-alpha, may also exert deleterious effects on cognitive function.[44]

Therefore, there are striking lines of evidence that support the causal relationship between Alzheimer's disease and disturbed glucose metabolism, insulin resistance and hyperinsulinemia.[45] Diabetes may affect cognition and lead to dementia through several different mechanisms. One of them is development of diabetes mellitus complications, such as hypertension, hyperlipidemia, CHD, stroke, and renal disease, all of which have been associated with cognitive dysfunction and Alzheimer's disease. Diabetes mellitus results in increased blood viscosity due to hyperglycemia, oxidative stress-induced endothelial dysfunction accompanied with loss of its nitric oxide-mediated properties, and alterations of the blood-brain barrier.[46] These abnormalities lead to disturbed cerebral perfusion and thus to cognitive impairment. Moreover, chronic exposure to hyperglycemia results in alterations in cerebral capillaries, such as basement membrane thickening,[47] leading to brain ischemia. Neuronal damage from cerebral atherosclerotic disease is another contributing factor.[34]

There is compelling evidence linking insulin to cognitive decline and dementia in diabetes mellitus. Interestingly, hippocampus is the main structure initially damaged in Alzheimer's disease.[48] Insulin promotes tau-protein (the main component of neurofibrillary tangles) phosphorylation, through inhibition of glycogen synthase kinase-3 enzyme activity.[49] Increased pancreatic islet amyloid has been positively correlated with Alzheimer's disease lesions in autopsy studies, supporting the notion of a common origin for Alzheimer's disease and diabetes mellitus.[50] Impaired cerebral insulin signalling pathways also seem to be involved in Alzheimer's disease,[51] resulting from reduced insulin levels and number of its receptors in the brain.[52] Thus, Alzheimer's disease could be characterized by insulin resistance of the brain.[53] Insulin is thought to play an important role in the metabolism of Aβ and tau-protein and consequently result in increased formation of senile plaques.[51] Insulin-degrading enzyme is a regulator of extracellular Aβ levels and is inhibited by insulin.[54] Increased insulin levels in insulin-resistant states lead to reduced degradation of Aβ through competitive inhibition of insulin-degrading enzyme in the brain.[54] Additionally, insulin stimulates Aβ secretion. The result is excessive Aβ deposition in senile plaques.

The exact mechanism by which hypertension may cause Alzheimer's disease has not been clearly elucidated. A possible suggestion is that hypertension leads to Alzheimer's disease through CVD, since it comprises a risk factor for subcortical white matter lesions commonly found in Alzheimer's disease, and has been associated with silent brain infarction; brain atrophy; atherosclerosis in the large cerebral and cervicocerebral arteries; endothelial and cellular dysfunction; and reduced cerebral blood flow.[43] There is also evidence that overactivation of the renin-angiotensin system might contribute to the pathogenesis of Alzheimer's disease.[55] Hypertension has been positively correlated with vascular permeability accompanied with protein extravasation, a common finding in the Alzheimer's disease brain, as well as with the number of neuritic plaques and neurofibrillary tangles in the brains of patients with Alzheimer's disease.[56]

The aforementioned features of MetS coexist and interact, thereby increasing the risk of developing atherosclerotic complications. These interactions provide a potential framework for an

improved understanding of the pathogenesis of Alzheimer's disease, especially in elderly patients with vascular risk factors (Figure), and may offer some promise toward the search for preventive and therapeutic treatments. In this respect, animal models currently being generated can be used to support studies that may provide mechanistic links between the MetS and neurodegeneration.[57]

INTERRELATIONS OF METABOLIC SYDROME AND ALZHEIMER'S DISEASE: DATA FROM CLINICAL STUDIES

The association of MetS with silent brain infarction[58] is in line with a vascular etiology of cognitive decline, since silent brain infarction has been found to predict clinical overt stroke[59] and reduced cognitive function (Table 2).[16] Kwon and colleagues[58] evaluated 1,588 neurologically healthy subjects who underwent brain magnetic resonance imaging and then assessed the associations both between full-blown MetS as well as its individual components and silent brain infarction. The results demonstrated a significant correlation of MetS with silent brain infarction (odds ratio [OR]: 2.18, 95% CI 1.38-3.44). The components of MetS that contributed significantly to the results were elevated blood pressure (OR: 3.75, 95% CI 2.05-6.85) and impaired fasting glucose (OR: 1.74, 95% CI 1.08-2.80).

A small number of clinical trials have been conducted in order to study the relationship between MetS and the risk of dementia. The Honolulu-Asia Aging Study[22] was a prospective cohort study of CVD that extended to a study of dementia 25 years after its beginning and revealed an increased risk of dementia with the clustering of MetS individual components (relative risk [RR]: 1.05, 95%CI 1.02-1.09). Specifically, body mass index, subscapular skinfold thickness and serum triglyceride showed a positive correlation with dementia (RR: 1.21, 95% CI 1.05-1.40, 1.21 95% CI 1.06-1.40 and 1.26 95% CI 1.09-1.45, respectively). This was the first study to evaluate the association between MetS as a whole and the risk of dementia with a long follow-up. However, most cases of dementia were of vascular origin.

In a 5-year, prospective observational study, Yaffe and colleagues[60] endeavored to determine whether MetS is a risk factor for cognitive impairment and to elucidate the role of inflammation in this association in 2,632 elderly individuals with a mean age of 74 years. High inflammation was defined as above median serum levels of interleukin-6 and C-reactive protein. Compared with those without the MetS, elders with MetS were more likely to have cognitive decline (RR: 1.20, 95% CI 1.02-1.41). There was a statistically significant interaction with inflammation and MetS (P=.03) on impaired cognition. Those with both MetS and high inflammation had an increased likelihood of cognitive impairment compared with those without MetS (multivariate adjusted RR: 1.66, 95% CI 1.19-2.32). Interestingly, par-

TABLE 2.
Clinical Studies Indicating an Association Between Metabolic Syndrome and Dementia

Study (year)	*Type of Study*	*N*	*Dementia/ Cognitive Impairment, RR (95% CI)*	*Alzheimer's Disease, RR (95% CI)*	*Vascular Dementia, RR (95% CI)*
Kalmijn et al (2000)[22]	Prospective, cohort	8,006	N/A	1.00 (0.94-1.05)	1.11 (1.05-1.18)
Yaffe et al (2004)[59]	Prospective, observational	2,632	1.20 (1.02-1.41)	N/A	N/A
Vanhanen et al (2006)[12] The Kuopio Study	Population-based	959	N/A	2.71 (1.44-5.10)	N/A
Razay et al (2007)[5]	Case-control	50 patients and 75 controls	N/A	3.2 (1.2-8.4)	N/A

RR=relative risk; N/A=not available.

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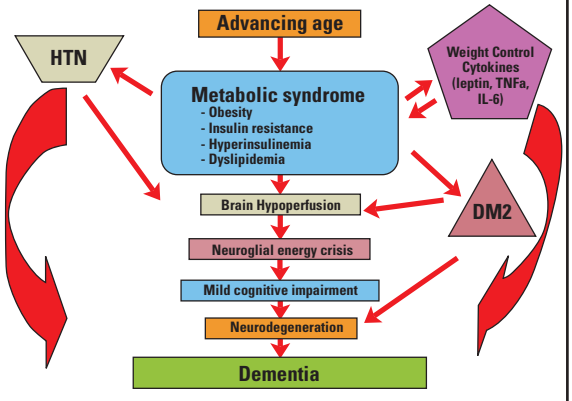
ticipants with MetS and low inflammation did not exhibit an increased likelihood of cognitive decline (multivariate adjusted RR: 1.08, 95% CI 1.19-2.32). These findings support the hypothesis that MetS is a risk factor for cognitive impairment in the elders, especially in those with high level of inflammation.

In another population-based study,[6] the Kuopio study, of 959 randomly selected elderly subjects (age range: 69–78 years) without dementia was designed to assess the relationship between MetS and Alzheimer's disease. The prevalence of Alzheimer's disease was higher in participants with the MetS (7.2% vs 2.8%, *P*<.001). MetS was significantly associated with Alzheimer's disease even after adjusting for apolipoprotein E4 phenotype, education, age, and total cholesterol (OR: 2.46, 95% CI 1.27-4.78). This association remained significant when diabetic patients were excluded from the multivariate analysis (OR: 3.26, 95% CI 1.45-7.27). This was the first study to investigate the relationship between MetS as an entity and specifically Alzheimer's disease (not dementia or cognitive decline, in general) and the results confirmed its initial hypothesis.

The relationship between MetS and Alzheimer's disease was verified in another study. Razay and colleagues[5] designed a case-control study of 50 consecutive patients with a diagnosis of probable Alzheimer's disease and 75 cognitively normal controls, in order to estimate the relationship between MetS and Alzheimer's disease. The results revealed a significant association of MetS with Alzheimer's disease (OR: 3.2, 95% CI 1.2-8.4, *P*=.02). Compared with controls, patients with Alzheimer's disease had a significantly larger waist circumference (*P*=.004), higher plasma glucose and triglyceride concentrations (*P*=.005 and *P*<.001, respectively) and lower plasma HDL cholesterol levels (*P*=.005), but they had lower mean systolic blood pressure (*P*=.001). In fact, when hypertension was excluded from the analysis, the association between MetS and Alzheimer's disease was strengthened (OR: 7.0, 95% CI 2.7-18.3, *P*<.001).

In a retrospective cohort study of 751 outpatients diagnosed with Alzheimer's disease who were followed for a mean period of 28 month,[62] the prevalence of MetS was 24.6% while the mortality rate throughout the study period was 14.0%. Multivariate analysis showed that MetS did not increased mortality in the study population after controlling for age, sex, the basic activities of daily living, and conduct disorders subscales from the Blessed scale, the Cumulative Illness Rating Scale for heart disease and the Folstein Mini-Mental State Examination. It is of note that patients with MetS were younger and presented lower degrees of cognitive and functional impairment, with greater organic comorbidity at the expense of heart diseases.

FIGURE.
Potential relationships between components of the metabolic syndrome and the development of Alzheimer's disease: *A link to a vascular etiology?*[61]



HTN=hypertension; TNFa; tumor necrosis factor-alpha; IL=interleukin; DM2=type 2 diabetes mellitus.

de la Torre JC. Is Alzheimer's disease a neurodegenerative or a vascular disorder? Data, dogma, and dialectics. *Lancet Neurol.* 2004;3:184-190. Adapted with permission from Elsevier Limited. Copyright 2004.

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CLINICAL IMPLICATIONS

The notion that atherosclerosis and Alzheimer's disease are independent but convergent disease processes may stimulate research of their common pathogenesis and contemplation of preventive and/or therapeutic strategies. Evaluation with simple clinical tools, such as a global cardiovascular risk assessment and the MetS, surmounts genetic risk factors (for example the e4 allele of the *apolipoprotein E* gene) in the identification and early intervention in subjects at risk. Prevention seems to be the most promising avenue for decreasing the incidence of atherosclerotic complications, including the two most common forms of senile dementia, Alzheimer's disease and vascular dementia. Collaboration between epidemiologists, internists, cardiologists, and neurologists toward the future design of cardiovascular trials incorporating pre-specified substudies of cognitive function should be

encouraged. Moreover, the use of treatments of proven efficacy in the process of atherosclerosis needs to be systematically tested in Alzheimer's disease. In this respect, recommendation should include a stepwise approach with lifestyle and diet modifications and pharmacologic therapy appropriately targeting hyperglycemia, hypertension, and dyslipidemia.

CONCLUSION

Alzheimer's disease, the most widespread type of dementia, is a progressive neurogenerative disease with epidemic proportions in contemporary societies. Despite its high prevalence and socioeconomic burden, the cause of the disease is unknown, explaining the lack of effective medication for its treatment. Thus far, the amyloid hypothesis has been the prevailing theory of Alzheimer's disease pathophysiology. However, several lines of evidence support a vascular hypothesis to be highly related to the pathology of Alzheimer's disease.[61] MetS, a constellation of interrelated metabolic derangements increasing the risk of CVD and diabetes, has been shown to be independently associated with Alzheimer's disease. Strategies toward early and effective risk factor management of (behavioral and/or drug treatment) could be of value in reducing cardiometabolic and the cognitive decline risk. ***CNS***

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