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Linking atherosclerosis to Alzheimer's disease: focus on biomarkers

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1. ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder with an important vascular component, ultimately resulting in dementia. Recent years have witnessed an enormous interest in the field of biomarkers in medicine both in the field of atherosclerosis and neurodegeneration. Numerous studies have recently reported altered levels of biomarkers of atherosclerotic vascular disease in patients with AD. This review provides an overview of clinical studies assessing biomarkers of atherosclerosis/vascular disease in the serum/plasma of patients with AD and highlights future directions in the field. The study of specific biomarkers of atherosclerosis in AD can contribute to identify different components of the pathophysiology and the complex mechanisms underlying the progression of the disease.

2. INTRODUCTION

Alzheimer's disease (AD) is a multifactorial progressive neurodegenerative brain disease resulting in dementia associated with the excessive deposition in the brain of amyloid β (Aβ) peptide plaques and neurofibrillary tangles (1, 2). Despite the central role played by Aβ deposition in the pathophysiology of this devastating dementing disorder, growing evidence suggests this mechanism as a necessary but not sufficient cause of its clinical manifestations (3-5). Hence, it has been postulated that other putative downstream mechanisms – including inflammation – can be equally important to AD pathogenesis (6, 7). In addition, vascular lesions, even if subtle, have been shown to exert significant effects on cognitive functioning if they coexist with AD pathology (8-10). There is also evidence suggesting that AD can be

Table 1. Summary of common biochemical markers of atherosclerosis found to be altered in AD and MCI discussed in this review

Markers	Pathophysiology	Current data
C-reactive protein	Higher levels are an aspecific marker of inflammation; may be involved in the inflammatory processes occurring in the early stages of AD	Conflicting evidence
Homocysteine	Folic acid intermediate; may be involved in neurodegeneration through disturbed methylation and/or redox potentials, amyloid and tau protein accumulation, apoptosis, and neuronal death	Conflicting evidence; potential genetic influences
Cystatin C	Lysosomal cysteine proteases inhibitor; involved in neurogenesis and neuroprotection from toxic insults, colocalizes with beta amyloid	Evidence suggests lower plasma CC levels in AD. Reduced baseline levels of CC were found to predict the conversion of MCI to AD. Conflicting data about CC plasma levels and cognitive impairment
Lipoprotein(a)	Macromolecular complex in human plasma strictly under genetic control; role in neuronal homeostasis through its expression in brain tissue.	Conflicting evidence; important potential genetic influences
Soluble RAGE	Multiligand receptor interacting with a number of proinflammatory ligands; increased Aβ influx at the blood brain barrier and vascular dysfunction.	Lowered levels in both MCI and AD
Osteoprotegerin	Pleiotropic cytokine; may be involved in silent cerebral ischemia	Conflicting evidence; potential genetic influences

associated with impaired cerebral perfusion (11). In this regard, atherosclerosis of the intracranial arteries has been shown to act as an independent risk factor for neurodegeneration (12). Accordingly, several studies have indicated that systemic atherosclerosis can increase AD pathology in a direct fashion (13-15). Alternatively, atherosclerosis and AD pathology may reflect a common underlying process leading to a relationship between the two pathologies (9).

Recent years have witnessed an enormous interest in the field of biomarker medicine both in relation to neurodegeneration (16, 17) and atherosclerosis (18, 19). Biological markers have been traditionally defined as cellular, biochemical or molecular alterations that are measurable in biological media such as human tissues, cells, or fluids. The availability of reliable biomarkers has tremendous potential to radically alter the diagnostic and monitoring strategies in the field of neurological and vascular disorders, and hopefully to effectively prognosticate patients with these conditions (17). Importantly, specific biomarkers can identify different components of the pathophysiology of AD. Recent studies have clearly shown that known biomarkers of atherosclerotic vascular disease are altered in patients with AD. It is also feasible that the combination of multiple biomarkers reflecting different pathophysiologic processes (Aβ and tau metabolism versus vascular components) can enhance risk stratification, as compared with using individual markers alone. In addition, cardiovascular biomarkers studied in patients with AD can shed more light on novel pathophysiological processes in AD with potential clinical significance.

In this review, we summarize the results of clinical studies assessing biomarkers of atherosclerosis/vascular disease in the serum/plasma of patients with AD in which these molecules have been shown to be altered (Table 1). Hopefully, this knowledge will help to clarify whether any of these biochemical markers is involved in the causal chain of AD progression or can mediate the effects of other risk factors for neurodegeneration.

3. C-REACTIVE PROTEIN

C-reactive protein (CRP) is a member of the pentraxin family of oligomeric serum proteins which has been conserved through evolution (20). A large body of evidence suggests that increased levels of CRP might serve as a marker of an increased risk of ischemic cardiac and cerebrovascular disease (21-23). Owing to the presence of an inflammatory component in AD, several studies have investigated the potential association between this condition and increased circulating CRP levels. Mancinella *et al.* (24) performed a cross-sectional study comparing markers of inflammation between 99 patients affected by dementia (34 with AD and 64 with vascular dementia) and 99 healthy comparison subjects. The results showed that patients with AD had higher CRP levels compared with both those with vascular dementia and healthy controls. Schuitemaker and coworkers (25) measured CRP, Abeta42, phospho-tau (p-tau) and total tau concentrations in serum and cerebrovascular fluid of 145 patients with probable AD and 67 patients with mild cognitive impairment. CRP levels were significantly higher in MCI compared with AD patients. Taken together, these findings suggest that inflammatory processes might be involved in early stages of AD, even before Abeta and tau changes. Despite these findings, it should be noted that conflicting evidence still exists on the issue of raised CRP levels in AD. In this regard, Nilsson *et al.* (26) have reported lower CRP levels in patients with AD compared with those with vascular dementia, mild cognitive impairment, or depression. In keeping with these results, O'Bryant *et al.* (27) reported that mean CRP levels were significantly decreased in a sample of AD from USA compared with cognitively healthy controls. In the longitudinal ULSAM-study conducted in a community-based sample of elderly men from Sweden, Sundelöf *et al.* (28) found no association between longitudinal changes in CRP levels and the risk of AD. Several explanations may account for these conflicting results. First, it has been shown that the analytical method employed (e.g., enzyme-linked immunossorbent assay versus nephelometry) can have a significant impact on the interpretation of CRP measurements (23). In this regard, international standardization of analytical kits would be highly desirable to ensure an increased degree of comparability between studies. Second, ethnicity has been shown to exert a confounding effect on CRP measurements in distinct studies worldwide (29). Therefore, interpretations that do not take into account the influence of ethnic factors are likely to be inaccurate. Third, different ways by which plasma samples are handled may represent a potential source of bias. Finally, CRP levels are known to be under a strict genetic control (30). Taken together, these

shortcomings should prompt large well-designed, methodologically-sound studies aimed to address the value of CRP both in the diagnosis and in the prognostication of patients with either AD or mild cognitive impairment.

4. HOMOCYSTEINE

Homocysteine is a thiol containing amino acid generated during the metabolism of methionine. It is converted by folate, vitamin B12 and B6 to cysteine, or can be recycled into methionine (31). A number of clinical studies have reported a statistically significant association between elevated circulating levels of homocysteine and an increased risk of cardiovascular and cerebrovascular disease, including stroke, peripheral arterial disease, and venous thrombosis (32, 33). Although the mechanisms behind this association remain only partly elucidated, these may include – among others – an increased oxidative inactivation of nitric oxide or inhibition of its production in endothelial cells (34). Besides vascular disorders, growing evidence suggests that homocysteine can act as a risk factor for cognitive impairment and AD (35). The mechanisms by which homocysteine affects cognitive function remain to be completely elucidated. Some authors have suggested that hyperhomocysteinemia in subjects with cognitive impairment or dementia is not a causal factor, but can merely reflect concomitant vascular disease (36). Interestingly, Gorgone *et al.* (37) have shown that the homozygous TT677 MTHFR genotype promotes plasma homocysteine increase which in turn may favour intima-media thickening in patients with cognitive impairment. Homocysteine can indeed promote neuronal damage through multiple mechanisms, including both a microvascular damage mediated by intima-media thickness increase and a direct neurotoxic effect. Moreover, homocysteine may cause disturbed methylation and/or redox potentials, thus promoting calcium influx, amyloid and tau protein accumulation, apoptosis, and neuronal death (35). Data derived from cross-sectional and longitudinal studies concerning peripheral levels of homocysteine in AD are conflicting. Cascalheira *et al.* (38) performed a case-control study of 19 individuals diagnosed with AD and 36 healthy controls. Multivariable logistic regression analysis identified homocysteine as an independent predictor of AD. Kivipelto *et al.* (39) analyzed homocysteine in a total of 228 non-demented subjects aged 75 years or more and reported that increased levels of this molecule were related to an increased risk of dementia and AD after a mean follow-up time of 6.7 years. Hooshmand and colleagues (40) examined the relation between serum levels of homocysteine and the risk of developing AD in a sample of 271 Finnish community-dwelling cognitively healthy elderly people. After a mean follow-up of 7 years, the authors found a 1.16-fold increase in the risk of developing AD for each 1 μmol/L increase in baseline homocysteine levels. Other authors, however, failed to demonstrate such a positive association. For example, Davis *et al.* (41) investigated levels of total homocysteine in 27 patients with AD and vascular dementia and 51 healthy controls. Levels of this molecule did not differ in patients with dementia compared with controls. In addition, homocysteine does not seem to be predictive of conversion of MCI to AD (42). In this regard, Siuda *et al.* (43) assessed whether vascular risk factors including hyperhomocysteinemia can predict the development of AD in a sample of 55 MCI patients. Although hyperhomocysteinemia was found more frequently in the MCI group, discriminant function analysis showed that this factor was not a significant predictor of progression to dementia within one year. The conflicting evidence available in the literature can be due to a number of different reasons. First, homocysteine levels can be heavily influenced by folic acid, vitamin B6 and B12 (44), a potential source of confounding which is not frequently accounted for. Similarly, it is known that homocysteine levels are regulated by genetic factors (45), possibly resulting in ethnicity-dependent findings. In any case, the identification of homocysteine as a potential vascular risk factor for AD is clinically relevant for therapeutic strategies designed to lower homocysteine. Importantly, McCampbell and colleagues (46) have recently shown that mutant amyloid precursor protein (APP)-expressing mice fed with high methionine levels show increased brain beta amyloid deposition, suggesting a close pathophysiological link between APP and methionine metabolism. In the clinical setting, Viswanathan *et al.* (47) have assessed whether vitamin supplementation-induced reduction of homocysteine could influence plasma Abeta levels in the Vitamin Intervention in Stroke Prevention (VISP) study. Of note, the authors found that homocysteine was strongly correlated with Abeta40 but not Abeta42 concentrations. However, treatment with high dose vitamins did not influence plasma levels of Abeta, despite their effect on lowering homocysteine. Future research is needed to assess the potential clinical usefulness of homocysteine-lowering strategies in patients with MCI and AD.

5. CYSTATIN C

Cystatin C (CC) is a strong endogenous inhibitor of lysosomal cysteine proteases, which are secreted by all nucleated cells (48). The unbalance between CC and cathepsins has been suggested to play an important role in the onset and progression of atherosclerosis and cardiovascular disease. Accordingly, the dynamic balance between proteases and CC is involved in a wide spectrum of physiological pathways, such as antigen presentation, neutrophil chemotaxis, tissue remodeling, degradation of extracellular matrix, cell proliferation, and vessel homeostasis (49). A severe decrease of CC expression has been reported in human atherosclerotic lesions compared to normal vessel wall (50). In addition, preliminary findings in apparently healthy subjects indicated the value of low CC levels for predicting the future development of heart failure, hypertension, diabetes, and metabolic syndrome (51).

In turn, multiple studies suggested that CC is a cofactor for neurogenesis and may have a protective role toward the development of neurodegenerative diseases, including AD (52). Immunohistochemical studies in AD brains have shown that CC colocalizes with beta amyloid (53). In addition, this molecule has been also reported to exert a proliferative effect on neural stem cells in vitro and

in vivo (54). A decrease of CC levels in the brain might therefore result both in the absence of protection from neurotoxic insults and in a defective stem cells-mediated regeneration (55).

Chuo *et al.* (56) investigated plasma levels of CC in AD and nondemented control individuals in Taiwan. The results showed that plasma CC levels were lower in AD patients than in controls. Importantly, Ghidoni and colleagues (57) have convincingly demonstrated that reduced baseline levels of CC predict the conversion of MCI to AD in a sample of Italian elderly individuals. Sundalof *et al.* (58) have also demonstrated that a 0.1-μmol/L decrease of CC between ages 70 and 77 years was associated with a 29% higher risk of incident AD in elderly men free of dementia at baseline.

However, the role of CC as a prognostic marker for neurodegeneration has been questioned. For example, Yaffe *et al.* (59) investigated the association of serum CC with cognitive function among 3030 subjects from the Health ABC study. Elderly people with high CC had worse baseline cognitive scores compared to those with intermediate or low level and more pronounced decline over 7 years. Such discrepancies could be due to the rather recent standardization and FDA approval of CC assays (60) which could have conditioned the interpretation of marker measurements in clinical laboratories. In addition, most previous studies were based on rather homogeneous subsets of elderly patients, frequently with a low sample size. The remaining evidences are based on ancillary investigations on prospective cohorts, which are characterized by large sample size but also by too heterogeneous case series (59). The selection and the size of the reference population are critical issues, since they could limit the inference of findings on biomarkers in this framework.

6. LIPOPROTEIN(a) AND APOLIPOPROTEIN(a)

Lipoprotein(a) [Lp(a)] is a macromolecular complex in human plasma, strictly under genetic control, consisting of a low density lipoprotein (LDL) particle to which the glycoprotein apolipoprotein(a) [apo(a)] is covalently bound by a single disulfide linkage (61). More than 34 apo(a) isoforms of different size have been detected in human plasma (62). Moreover, operational null alleles, defined by absence of apo(a) isoforms from immunoblots [apo(a) null phenotype], have been described (63). The physiological role of Lp(a) in humans is still unclear (61). Because of the high homology between plasminogen and apo(a), it is feasible that Lp(a) plays a role in the coagulation system, especially into thrombosis and impaired fibrinolysis processes (64). It can also accumulate in the arterial walls and cerebral vessels (65). Different studies have identified elevated Lp(a) levels and short apo(a) size as emerging risk factors for atherosclerotic diseases such as coronary artery disease and stroke, although some conflicting evidence still exists (66, 67). Importantly, Lp(a) has also been suggested to play a role in the onset and progression of dementia. Lp(a) may increase the risk for cognitive decline through its association with atherosclerosis and silent cerebrovascular disease (68). Alternatively, it can play a direct role in neuronal homeostasis through its expression in brain tissue (69).

In a seminal study, Mooser *et al.* (70) demonstrated that serum Lp(a) levels were associated with a progressive, age-dependent increased risk for late-onset Alzheimer's disease in carriers of the apoE epsilon4 allele. Emanuele *et al.* (69) analyzed plasma Lp(a) levels and apo(a) isoform size in 73 sporadic AD patients compared with 73 age- and gender-matched healthy controls. The distribution of apo(a) isoforms and Lp(a) concentrations were similar in the two groups. However, AD subjects with the apo(a) null phenotype had a significantly higher mean age at onset than those who expressed at least one apo(a) isoform (69). Another case-control study compared Lp(a) plasma levels and the distribution of apo(a) phenotypes in 50 VaD patients, 162 sporadic AD patients, 95 non-demented stroke patients, and 105 normal controls (68). The authors found that the presence of at least one small-sized apo(a) isoform significantly increased the risk of AD. Solfrizzi and colleagues (71) investigated Lp(a) serum concentrations in 61 patients with a diagnosis of probable AD and in 63 healthy unrelated age matched controls. Lp(a) serum concentrations were significantly associated in a non-linear relation with an increased risk for AD, independently of other confounders (71). However, this relation was not confirmed in a small-sized study conducted by Urakami *et al.* (72) in Japanese AD patients. It is possible that different experimental designs, different number and characteristics of subjects recruited, medical treatments, lack of standardization of methods for the determination of Lp(a) levels and different ways in which plasma samples are handled might at least partially explain the differences among the studies (73).

7. SOLUBLE RECEPTOR FOR ADVANCED GLYCATION ENDPRODUCTS (sRAGE)

The receptor for advanced glycation endproducts (RAGE) is a cell-surface member of the immunoglobulin superfamily and a multiligand receptor interacting with a number of different proinflammatory ligands, including advanced glycation endproducts, S100 calcium-binding proteins, high mobility group box 1, and amyloid beta-peptide (74). The interaction of cell-surface RAGE with its proinflammatory ligands results in an increased oxidative stress and activation of NF-κB, which in turn leads to increased expression of proinflammatory genes and further generation of oxygen radicals (75, 76). RAGE has secretory isoforms referred to as soluble RAGE (sRAGE), which comprise the extracellular ligand-binding domain but are lacking the cytosolic and transmembrane domains (77). Soluble RAGE has the same ligand binding specificity of cell-bound RAGE and may serve as a decoy abrogating cellular activation in endothelial cells (78). The association of sRAGE levels with a pathological state, was first reported by Falcone and colleagues (79), who demonstrated that lower sRAGE levels were associated with a increased risk of coronary artery disease. Subsequently, serum levels of total sRAGE have been shown to be associated with a range of vascular pathologies including essential hypertension, coronary artery disease, and intimal-medial thickening of the arteries (80, 81).

Importantly, a number of recent studies have demonstrated that RAGE plays multiple roles in the pathogenesis of neurodegenerative disorders, like AD. This may be ascribed to the interaction of this receptor with amyloid beta peptide which activates a positive feedback mechanism governing RAGE expression (82, 83). The adverse consequences of RAGE interaction with amyloid beta peptide include perturbation of neuronal properties and functions, amplification of glial inflammatory responses, elevation of oxidative stress and amyloidosis, increased amyloid beta peptide influx at the blood brain barrier and vascular dysfunction (83). It has also been proposed that RAGE activation by amyloid beta peptide could take place at an early stage of AD resulting in early neuronal dysfunction (82, 83). Intriguingly, Chaney and colleagues (84) have shown that the binding of soluble amyloid beta peptide to soluble RAGE inhibits further aggregation of amyloid beta peptides. Taken together, this observation has prompted clinical studies aimed at investigating whether sRAGE could serve as a biomarker of AD in humans. Emanuele *et al.* (85) designed a cross-sectional study of 152 Italian patients with a clinical diagnosis of AD, 91 with vascular dementia and 161 control subjects. Plasma levels of sRAGE were lower in patients with AD compared with both vascular dementia and controls. In addition, the authors demonstrated that sRAGE levels below 776 pg/mL were significantly and independently associated with vascular dementia and, more strongly, AD (85). Ghidoni *et al.* (86) have recently investigated sRAGE levels in Italian patients with AD, mild cognitive impairment, and cognitive healthy subject. The highest sRAGE levels were detected in healthy controls and the lowest in the AD group, with intermediate concentrations in the MCI group. The carriage of the APOE e4 allele did not influence sRAGE levels in each study group. Importantly, the authors highlighted the fact that very low sRAGE levels were associated with an early onset of cognitive impairment (86). Interestingly, Li *et al.* (87) demonstrated that plasma sRAGE levels were lower in Chinese AD patients than in normal elderly controls, and the presence of the RAGE 82S risk allele was associated with reduced plasma sRAGE and a fast cognitive deterioration. However, Hernanz *et al.* (88) did not find significant differences in serum levels of sRAGE in AD or patients with mild cognitive impairment from Spain compared to controls. At present, we do not know whether sRAGE levels in serum/plasma could be mechanistically related to AD by reflecting neural tissue RAGE expression. However, previous studies have already reported an upregulation of neuronal RAGE in AD (89). Second, the enzyme-linked immunosorbent assay used in previous studies quantifies concentrations of total sRAGE in serum/plasma. This assay cannot differentiate between native secretory RAGE isoforms and soluble RAGE that results from the cleavage of the cell-surface receptor by metalloproteinases (80). Third, sRAGE levels are known to be influenced by both ethnicity and genetic factors, and these issues should be taken into account for future clinical studies of sRAGE in AD (90).

8. OSTEOPROTEGERIN

Osteoprotegerin (OPG), a tumor necrosis factor receptor family member, is a soluble glycoprotein expressed in most human tissues (91). OPG acts as a decoy receptor for the receptor activator for nuclear factor κB (RANK) ligand (RANKL) and has been shown to regulate a variety of pathophysiological processes such as inflammation and apoptosis (92). Numerous clinical studies have consistently reported a significant association between high serum levels of OPG and coronary atherosclerosis, vascular calcification, heart failure, and cardiovascular mortality (93). The exact mechanisms by which OPG influences cardiovascular pathophysiology may involve endothelial and ventricular dysfunction, inflammation and calcification (93). Recent research also suggests that OPG may exert an important anti-apoptotic effect on neural tissues, indicating a potential role of this molecule in neurodegeneration (94). Of note, OPG has been reported to be expressed in the spinal cord and in fetal mouse and human brain (95).

Emanuele *et al.* (96) investigated OPG concentrations in an Italian sample of 39 patients with vascular dementia, 36 AD patients, and 39 non-demented controls. OPG concentrations were significantly higher in both vascular dementia and AD compared to non-demented controls. After adjustment for confounding factors including the APOE ε4 allele, plasma OPG levels remained independently associated with the presence of VaD and AD (96). Importantly, in the Framingham Heart Study, OPG levels were inversely associated with total brain volume, thus confirming that increased OPG can be associated with greater brain atrophy than expected for age (97). However, increased OPG plasma levels in patients with AD were not confirmed in a small-sample sized cross-sectional study by Luckhaus and colleagues (98). The latter negative result could be possibly due to the statistical limitations in relation to limited sample size. Further research assessing OPG in the cerebrospinal fluid may shed more light on the potential role played by this molecule in linking vascular disease and neurodegeneration.

9. MISCELLANEOUS MARKERS

Several other miscellaneous markers of atherosclerotic vascular disease have been investigated in AD patients. Semicarbazide-sensitive amine oxidase (SSAO) is the common name for a group of enzymes which play a role in vascular endothelial damage and in progression of atherosclerosis through the conversion of endogenous amines into cytotoxic aldehydes, ammonia and hydrogen peroxide (99). In patients with diabetes mellitus and chronic heart failure, plasma activity appears to rise in parallel with disease severity (100). Unzeta *et al.* (101) have shown that SSAO is hyperexpressed in the cerebrovascular tissue of AD patients with cerebral amyloid angiopathy and colocalizes with beta-amyloid deposits. Interestingly, increased cerebral expression of SSAO was mirrored by a higher SSAO activity in plasma of severe AD patients (101). These results suggested that SSAO may contribute to the vascular damage associated to AD. These findings were subsequently confirmed by Jiang *et al.* (102) who demonstrated a strong colocalization of SSAO with beta-amyloid deposits on the blood vessels in AD brains. The authors also showed that SSAO-mediated

deamination increases the deposition of beta-amyloid onto blood vessel walls (102). Taken together, these results support the hypothesis that cerebral vascular SSAO-catalyzed deamination contributes to cerebral amyloid angiopathy in AD brains.

A large body of evidence suggests that iron and copper play a multifaceted role in both atherosclerosis and AD. Previous studies have shown that even modest levels of stored iron can promote cardiovascular disease while sustained iron depletion is protective against it (103). In addition, the imbalance in copper metabolism may contribute to the risk of atherosclerosis or be a consequence of an acute phase response which increases vascular risk (104). Interestingly, Brewer (105) has suggested that iron and copper can act as a link between vascular damage and AD through the excess production of damaging reactive oxygen species through Fenton chemistry. Very recently, Liu *et al.* (106) have reported that iron delays the formation of well ordered aggregates of Aβ and so promotes its toxicity in AD. In addition, a meta-analysis by Bucossi *et al.* (107) has convincingly demonstrated that higher copper levels can be found in serum and plasma of AD patients.

10. IMAGING BIOMARKERS OF ATHEROSCLEROSIS IN ALZHEIMER'S DISEASE

Besides serum/plasma markers of atherosclerosis, there is a growing interest in imaging biomarkers of atherosclerosis in relation to the presence of AD. Carotid arteries intima-media thickness (IMT) and plaque index (PI) are two common surrogate measures of atherosclerotic burden which can be measured by means of ultrasound. Silvestrini *et al.* (108) have recently investigated the correlation between the progression of carotid atherosclerosis and the evolution of cognitive impairment in AD patients. The results showed a linear association between progression of carotid wall changes and of cognitive decline. Similarly, Jurasic *et al.* (109) have also reported that the results of Mini Mental State Examination of AD patients relate to changes of arterial stiffness of the common carotid artery. It is noteworthy that de la Torre (110) has shown that regional cerebral hypoperfusion as assessed by single-photon emission CT (SPECT) or from uptake of injected fluorine-18-labelled fluorodeoxyglucose with PET (positron emission tomography) is one of the earliest, if not the earliest, marker of AD symptoms.

11. OPEN ISSUES

According to traditional thinking, biomarkers delineate variances from normal biology when they rise beyond a normal range in response to one or more pathologic events. Most of the studies in this review reported an alteration of biomarkers of atherosclerosis in the setting of AD with good sensitivity and specificity according to the classifier's data. However, a majority of the studies reported here have inherent shortcomings including small sample size, poor choice of controls (rarely reflecting the clinical setting in which the test would be used), data-dependent thresholds and lack of validation. In addition, it is not yet known whether these molecules could serve as antecedent biomarkers (identifying the inherent or existing risk of developing AD) or prognostic biomarkers (predicting the natural history of disease, including response to treatment) (111).

12. PERSPECTIVES

A variety of serum/plasma biomarkers of atherosclerosis have been shown to be altered in patients with AD and MCI (17, 112). Whether these markers may have implications for early screening, detection, and diagnosis of AD remains to be established. Crucial remaining problems, such as easy reliability, acceptance and application of the test, cost-effectiveness, need to be resolved. Hopefully, blood-based testing will most likely be the prerequisite to future sensitive screening of large populations at risk of AD and the baseline in a diagnostic flow approach to AD, especially in individuals bearing traditional cardiovascular risk factors. For a complex disease such as AD, combining multiple biomarkers from different pathophysiological pathways may increase the sensitivity and specificity of diagnosis of cognitive decline (113, 114). All identified biomarkers are still in the preclinical testing stage, and need much more validation in large population based longitudinal studies. Obviously, these available data on altered levels of biochemical markers of atherosclerosis in patients with AD strongly support the idea of a vascular component in the pathogenesis of this devastating neurodegenerative disease. Starting from these premises, future studies of clinical cohorts of AD patients should aim to perform a detailed vascular characterization of the subjects, including imaging markers of subclinical carotid atherosclerosis and brain vascular damage. An accurate analysis of clinical and biochemical vascular markers should thus form the basis for the research agenda for future studies in the field.

13. REFERENCES

1. R. L. Nussbaum and C. E. Ellis: Alzheimer's disease and Parkinson's disease. *N Engl J Med*, 348(14), 1356-64 (2003)

2. A. Burns, E. J. Byrne and K. Maurer: Alzheimer's disease. *Lancet*, 360(9327), 163-5 (2002)

3. R. Altman and J. C. Rutledge: The vascular contribution to Alzheimer's disease. *Clin Sci (Lond)*, 119(10), 407-21 (2010)

4. R.D. Bell and B. V. Zlokovic: Neurovascular mechanisms and blood-brain barrier disorder in Alzheimer's disease. *Acta Neuropathol*, 118(1), 103-13 (2009)

5. B. V. Zlokovic: Neurovascular mechanisms of Alzheimer's neurodegeneration. *Trends Neurosci*, 28(4), 202-8 (2005)

6. S. Vasto, G. Candore, G. Duro, D. Lio, M. P. Grimaldi and C. Caruso: Alzheimer's disease and genetics of inflammation: a pharmacogenomic vision. *Pharmacogenomics*, 8(12), 1735-45 (2007)

7. G. Candore, C. R. Balistreri, M. P. Grimaldi, S. Vasto, F. Listì, M. Chiappelli, F. Licastro, D. Lio and C. Caruso: Age-related inflammatory diseases: role of genetics and gender in the pathophysiology of Alzheimer's disease. *Ann N Y Acad Sci*, 1089, 472-86 (2006)

8. J.C. de la Torre: Vascular risk factor detection and control may prevent Alzheimer's disease. *Ageing Res Rev*, 9(3), 218-25 (2010)

9. J.C. de la Torre: The vascular hypothesis of Alzheimer's disease: bench to bedside and beyond. Neurodegener Dis, 7(1-3), 116-21 (2010)

10. S.A. Ligthart, E. P. Moll van Charante, W. A. Van Gool and E. Richard: Treatment of cardiovascular risk factors to prevent cognitive decline and dementia: a systematic review. Vasc Health Risk Manag, 6, 775-85 (2010)

11. T.C. de Toledo Ferraz Alves, L. K. Ferreira, M. Wajngarten and G. F. Busatto: Cardiac disorders as risk factors for Alzheimer's disease. J Alzheimers Dis, 20(3), 749-63 (2010)

12. T.G. Beach, J. R. Wilson, L. I. Sue, A. Newell, M. Poston, R. Cisneros, Y. Pandya, C. Esh, D. J. Connor, M. Sabbagh, D. G. Walker and A. E. Roher: Circle of Willis atherosclerosis: association with Alzheimer's disease, neuritic plaques and neurofibrillary tangles. Acta Neuropathol, 113(1), 13-21 (2007)

13. L. S. Honig, W. Kukull and R. Mayeux: Atherosclerosis and AD: analysis of data from the US National Alzheimer's Coordinating Center. Neurology, 64(3), 494-500 (2005)

14. C. Qiu, W. Xu, B. Winblad and L. Fratiglioni: Vascular risk profiles for dementia and Alzheimer's disease in very old people: a population-based longitudinal study. J Alzheimers Dis, 20(1), 293-300 (2010)

15. D. F. Cechetto, V. Hachinski and S. N. Whitehead: Vascular risk factors and Alzheimer's disease. Expert Rev Neurother, 8(5), 743-50 (2008)

16. M. Ewers, M. M. Mielke and H. Hampel: Blood-based biomarkers of microvascular pathology in Alzheimer's disease. Exp Gerontol, 45(1), 75-9 (2010)

17. K. Blennow, H. Hampel, M. Weiner and H. Zetterberg: Cerebrospinal fluid and plasma biomarkers in Alzheimer disease. *Nat Rev Neurol*, 6(3), 131-44 (2010)

18. R.R. Packard and P. Libby: Inflammation in atherosclerosis: from vascular biology to biomarker discovery and risk prediction. *Clin Chem*, 54(1), 24-38 (2008)

19. W. Zhou, H. Chai, R. Ding and H. Y. Lam: Distribution of inflammatory mediators in carotid and femoral plaques. *J Am Coll Surg*, 211(1), 92-8 (2010)

20. J. M. Noble, J. J. Manly, N. Schupf, M. X. Tang, R. Mayeux and J. A. Luchsinger: Association of C-reactive protein with cognitive impairment. *Arch Neurol*, 67(1), 87-92, (2010)

21. D. Conen and P. M. Ridker: Clinical significance of high-sensitivity C-reactive protein in cardiovascular disease. *Biomark Med*, 1(2), 229-41 (2007)

22. S. Mora, K. Musunuru and R. S. Blumenthal: The clinical utility of high-sensitivity C-reactive protein in cardiovascular disease and the potential implication of JUPITER on current practice guidelines. *Clin Chem*, 55(2), 219-28 (2009)

23. E. T. Yeh: High-sensitivity C-reactive protein as a risk assessment tool for cardiovascular disease. *Clin Cardiol*, 28(9), 408-12 (2005)

24. A. Mancinella, M. Mancinella, G. Carpinteri, A. Bellomo, C. Fossati, V. Gianturco, A. Iori, E. Ettorre, G. Troisi and V. Marigliano: Is there a relationship between high C-reactive protein (CRP) levels and dementia? *Arch Gerontol Geriatr*, 49 Suppl 1, 185-94 (2009)

25. A. Schuitemaker, M. G. Dik, R. Veerhuis, P. Scheltens, N. S. Schoonenboom, C. E. Hack, M .A. Blankenstein and C. Jonker: Inflammatory markers in AD and MCI patients with different biomarker profiles. *Neurobiol Aging*, 30(11), 1885-9 (2009)

26. K. Nilsson, L. Gustafson and B. Hultberg: C-reactive protein: vascular risk marker in elderly patients with mental illness. *Dement Geriatr Cogn Disord*, 26(3), 251-6 (2008)

27. S. E. O'Bryant, S. C. Waring, V. Hobson, J. R. Hall, C. B. Moore, T. Bottiglieri, P. Massman and R. Diaz-Arrastia: Decreased C-reactive protein levels in Alzheimer disease. *J Geriatr Psychiatry Neurol*, 23(1), 49-53 (2010)

28. J. Sundelöf, L. Kilander, J. Helmersson, A. Larsson, E. Rönnemaa, M. Degerman-Gunnarsson, H. Basun, L. Lannfelt and S. Basu: Systemic inflammation and the risk of Alzheimer's disease and dementia: a prospective population-based study. *J Alzheimers Dis*, 18(1), 79-87 (2009)

29. T. L. Gruenewald, S. Cohen, K. A. Matthews, R. Tracy and T. E. Seeman: Association of socioeconomic status with inflammation markers in black and white men and women in the Coronary Artery Risk Development in Young Adults (CARDIA) study. *Soc Sci Med*, 69(3), 451-9 (2009)

30. W. Schumacher, J. Cockcroft, N. H. Timpson, C. M. McEniery, J. Gallacher, A. Rumley, G. Lowe, G. D. Smith, I. B. Wilkinson and Y. Ben-Shlomo: Association between C-reactive protein genotype, circulating levels, and aortic pulse wave velocity. *Hypertension,* 53(2), 150-7 (2009)

31. R. Ientile, M. Currò, N. Ferlazzo, S. Condello, D. Caccamo and F. Pisani: Homocysteine, vitamin

determinants and neurological diseases. *Front Biosci (Schol Ed)*, 2, 359-72 (2010)

32. M. N. Di Minno, E. Tremoli, A. Coppola, R. Lupoli and G. Di Minno: Homocysteine and arterial thrombosis: Challenge and opportunity. *Thromb Haemost*, 103, 942-61 (2010)

33. A. S. Wierzbicki: Homocysteine and cardiovascular disease: a review of the evidence. *Diab Vasc Dis Res*, 4(2),143-50 (2007)

34. K. T. Williams and K. L. Schalinske: Homocysteine metabolism and its relation to health and disease. *Biofactors*, 36(1), 19-24 (2010)

35. T. B. Shea, J. Lyons-Weiler and E. Rogers: Homocysteine, folate deprivation and Alzheimer neuropathology. *J Alzheimers Dis*, 4(4), 261-7 (2002)

36. M. P. Mattson and T. B. Shea: Folate and homocysteine metabolism in neural plasticity and neurodegenerative disorders. *Trends Neurosci*, 26, 137-46 (2003)

37. G. Gorgone, F. Ursini, C. Altamura, F. Bressi, M. Tombini, G. Curcio, P. Chiovenda, R. Squitti, M. Silvestrini, R. Ientile, F. Pisani, P.M. Rossini and F. Vernieri: Hyperhomocysteinemia, intima-media thickness and C677T MTHFR gene polymorphism: a correlation study in patients with cognitive impairment. *Atherosclerosis*, 206(1), 309-13 (2009)

38. J.F. Cascalheira, S. S. João, S. S. Pinhanços, R. Castro, M. Palmeira, S. Almeida, M. C. Faria and F. C. Domingues: Serum homocysteine: interplay with other circulating and genetic factors in association to Alzheimer's type dementia. *Clin Biochem*, 42(9), 783-90 (2009)

39. M. Kivipelto, S. Annerbo, J. Hultdin, L. Bäckman, M. Viitanen, L. Fratiglioni and J. Lökk: Homocysteine and holo-transcobalamin and the risk of dementia and Alzheimers disease: a prospective study. *Eur J Neurol*, 16(7), 808-13 (2009)

40. B. Hooshmand, A. Solomon, I. Kåreholt, J. Leiviskä, M. Rusanen, S. Ahtiluoto, B. Winblad, T. Laatikainen, H. Soininen and M. Kivipelto: Homocysteine and holotranscobalamin and the risk of Alzheimer disease: a longitudinal study. *Neurology*, 75(16), 1408-14 (2010)

41. G. Davis, N. Baboolal, S. Nayak and A. McRae: Sialic acid, homocysteine and CRP: potential markers for dementia. *Neurosci Lett*, 465(3), 282-4 (2009)

42. I.A. van Rossum, S. Vos, R. Handels and P.J. Visser: Biomarkers as predictors for conversion from mild cognitive impairment to Alzheimer-type dementia: implications for trial design. *J Alzheimers Dis*, 20(3), 881-91 (2010)

43. J. Siuda, A. Gorzkowska, M. Patalong-Ogiewa, E. Krzystanek, E. Czech, B. Wiechuła, W. Garczorz, A. Danch, B. Jasińska-Myga and G. Opala: From mild cognitive impairment to Alzheimer's disease - influence of homocysteine, vitamin B12 and folate on cognition over time: results from one-year follow-up. *Neurol Neurochir Pol*, 43(4), 321-9 (2009)

44. H. McNulty, K. Pentieva, L. Hoey and M. Ward: Homocysteine, B-vitamins and CVD. *Proc Nutr Soc*, 67(2), 232-7 (2008)

45. K. Miyaki: Genetic polymorphisms in homocysteine metabolism and response to folate intake: a comprehensive strategy to elucidate useful genetic information. *J Epidemiol*, 20(4), 266-70 (2010)

46. A. McCampbell, K. Wessner, M. W. Marlatt, C. Wolffe, D. Toolan, A. Podtelezhnikov, S. Yeh, R. Zhang, P. Szczerba, K. Q. Tanis, J. Majercak, W. J. Ray and M. Savage: Induction of Alzheimer's-like changes in brain of mice expressing mutant APP fed excess methionine. *J Neurochem*, 116(1), 82-92 (2011)

47. A. Viswanathan, S. Raj, S. M. Greenberg, M. Stampfer, S. Campbell, B. T. Hyman and M. C. Irizarry: Plasma Abeta, homocysteine, and cognition: the Vitamin Intervention for Stroke Prevention (VISP) trial. *Neurology*, 72(3), 268-72 (2009)

48. M. Mussap and M. Plebani: Biochemistry and clinical role of human cystatin C. *Crit Rev Clin Lab Sci,* 41(5-6), 467-550 (2004)

49. E. Bengtsson, J. Nilsson and S. Jovinge: Cystatin C and cathepsins in cardiovascular disease. *Front Biosci*, 13, 5780-6 (2008)

50. J. Liu, G.K. Sukhova, J. S. Sun, W. H. Xu, P. Libby and G.P. Shi: Lysosomal cysteine proteases in atherosclerosis. *Arterioscler Thromb Vasc Biol*, 24(8), 1359-66 (2004)

51. P. Muntner, D. Mann, J. Winston, S. Bansilal and M. E. Farkouh: Serum cystatin C and increased coronary heart disease prevalence in US adults without chronic kidney disease. *Am J Cardiol*, 102(1), 54-7(2008)

52. S. Gauthier, G. Kaur, W. Mi, B. Tizon and E. Levy: Protective mechanisms by cystatin C in neurodegenerative diseases. *Front Biosci (Schol Ed)*, 3, 541-54 (2011)

53. A. Nagai, M. Terashima, A. M. Sheikh, Y. Notsu, K. Shimode, S. Yamaguchi, S. Kobayashi, S. U. Kim and J. Masuda: Involvement of cystatin C in pathophysiology of CNS diseases. *Front Biosci*, 13, 3470-9 (2008)

54. P. Taupin, J. Ray, W. H. Fischer, S. T. Suhr, K. Hakansson, A. Grubb and F. H. Gage: FGF-2-responsive neural stem cell proliferation requires CCg, a novel autocrine/paracrine cofactor. *Neuron*, 28(2), 385-97 (2000)

55. B. Tizon, E. M. Ribe, W. Mi, C. M. Troy and E. Levy: Cystatin C protects neuronal cells from amyloid-beta-induced toxicity. *J Alzheimers Dis*, 19(3), 885-94 (2010)

56. L.J. Chuo, W. H. Sheu, M. C. Pai and Y. M. Kuo: Genotype and plasma concentration of cystatin C in patients with late-onset alzheimer disease. *Dement Geriatr Cogn Disord,* 23(4), 251-7 (2007)

57. R. Ghidoni, L. Benussi, M. Glionna, S. Desenzani, V. Albertini, E. Levy, E. Emanuele and G. Binetti: Plasma cystatin C and risk of developing Alzheimer's disease in subjects with mild cognitive impairment. *J Alzheimers Dis*, 22(3), 985-91 (2010)

58. J. Sundelöf, J. Arnlöv, E. Ingelsson, J. Sundström, S. Basu, B. Zethelius, A. Larsson, M. C. Irizarry, V. Giedraitis, E. Rönnemaa, M. Degerman-Gunnarsson, B. T. Hyman, H. Basun, L. Kilander and L. Lannfelt: Serum cystatin C and the risk of Alzheimer disease in elderly men. *Neurology*, 71(14), 1072-9 (2008)

59. K. Yaffe, K. Lindquist, M. G. Shlipak, E. Simonsick, L. Fried, C. Rosano, S. Satterfield, H. Atkinson, B. G. Windham and M. Kurella-Tamura: Cystatin C as a marker of cognitive function in elders: findings from the health ABC study. *Ann Neurol*, 63(6), 798-802 (2008)

60. E. Marrer and F. Dieterle: Impact of biomarker development on drug safety assessment. *Toxicol Appl Pharmacol*, 243(2):167-79 (2010)

61. F. Galvano, M. Malaguarnera, M. Vacante, M. Motta, C. Russo, G. Malaguarnera, N. D'Orazio and L. Malaguarnera: The physiopathology of lipoprotein (a). *Front Biosci (Schol Ed),* 2, 866-75 (2010)

62. S. Erqou, A. Thompson, E. Di Angelantonio, D. Saleheen, S. Kaptoge, S. Marcovina and J. Danesh: Apolipoprotein(a) isoforms and the risk of vascular disease: systematic review of 40 studies involving 58,000 participants. *J Am Coll Cardiol*, 55(19), 2160-7 (2010)

63. E. Emanuele, E. Peros, C. Tomaino, E. Feudatari, L. Bernardi, G. Binetti, R. Maletta, A. D'Angelo, L. Montagna, A. C. Bruni and D. Geroldi: Apolipoprotein(a) null phenotype is related to a delayed age at onset of Alzheimer's disease. *Neurosci Lett*, 357(1), 45-8 (2004)

64. W. Discepolo, T. Wun and L. Berglund: Lipoprotein(a) and thrombocytes: potential mechanisms underlying cardiovascular risk. *Pathophysiol Haemost Thromb*, 35(3-4), 314-21 (2006)

65. A. D'Angelo, D. Geroldi, M. A. Hancock, V. Valtulina, A. I. Cornaglia, C. A. Spencer, E. Emanuele, A. Calligaro, M. L. Koschinsky, P. Speziale and L. Visai: The apolipoprotein(a) component of lipoprotein(a) mediates binding to laminin: contribution to selective retention of lipoprotein(a) in atherosclerotic lesions. *Biochim Biophys Acta*, 1687(1-3), 1-10 (2005)

66. V. Bermúdez, N. Arráiz, D. Aparicio, E. Rojas, D. Gotera, X. Guerra, R. Canelón, J. Faría, L. Sorell, A. Amell, N. Reyna, M. Cabrera, E. Mengual, R. Cano, C. Cano and M. Velasco: Lipoprotein(a): from molecules to therapeutics. *Am J Ther*, 17(3), 263-73 (2010)

67. E. Anuurad, M. B. Boffa, M. L. Koschinsky and L. Berglund L: Lipoprotein(a): a unique risk factor for cardiovascular disease. *Clin Lab Med*, 26(4), 751-72 (2006)

68. E. Emanuele, E. Peros, C. Tomaino, E. Feudatari, L. Bernardi, G. Binetti, R. Maletta, G. Micieli, A. C. Bruni and D. Geroldi D: Relation of apolipoprotein(a) size to alzheimer's disease and vascular dementia. *Dement Geriatr Cogn Disord*, 18(2), 189-96 (2004)

69. E. Emanuele, E. Peros, C. Tomaino, E. Feudatari, L. Bernardi, G. Binetti, R. Maletta, G. Micieli, A. C. Bruni and D. Geroldi; Association between small apolipoprotein(a) isoforms and frontotemporal dementia in humans. *Neurosci Lett*, 353(3), 201-4 (2003)

70. V. Mooser, N. Helbecque, J. Miklossy, S. M. Marcovina, P. Nicod and P. Amouyel: Interactions between apolipoprotein E and apolipoprotein(a) in patients with late-onset alzheimer disease. *Ann Intern Med,* 132(7), 533-7 (2000)

71. V. Solfrizzi, F. Panza, A. D'Introno, A. M. Colacicco, C. Capurso, A. M. Basile and A. Capurso: Lipoprotein(a), apolipoprotein E genotype, and risk of Alzheimer's disease. *J Neurol Neurosurg Psychiatry,* 72(6), 732-6 (2002)

72. K. Urakami, K. Wada-Isoe, Y. Wakutani, K. Ikeda, Y. Ji, K. Yamagata, H. Kowa, A. Okada, Y. Adachi and K. Nakashima: Lipoprotein(a) phenotypes in patients with vascular dementia. *Dement Geriatr Cogn Disord*, 11(3), 135-8. (2000)

73. C. Gazzaruso, A. Garzaniti, P. Buscaglia, G. Bonetti, C. Falcone, P. Fratino, G. Finardi and D. Geroldi: Association between apolipoprotein(a) phenotypes and coronary heart disease at a young age. *J Am Coll Cardiol*, 33(1), 157-63 (1999)

74. P. Alexiou, M. Chatzopoulou, K. Pegklidou and V. J. Demopoulos : RAGE: a multi-ligand receptor unveiling novel insights in health and disease. *Curr Med Chem*, 17(21), 2232-52 (2010)

75. A.Z. Kalea, A. M. Schmidt and B. I. Hudson: RAGE: a novel biological and genetic marker for vascular disease. *Clin Sci (Lond)*, 116(8), 621-37 (2009)

76. S.F. Yan, Y. Naka, B. I. Hudson, K. Herold, S. D. Yan, R. Ramasamy and A. M. Schmidt: The ligand/RAGE axis: lighting the fuse and igniting vascular stress. *Curr Atheroscler Rep*, 8(3), 232-9 (2006)

77. S. Yamagishi and T. Matsui: Soluble form of a receptor for advanced glycation end products (sRAGE) as a biomarker. *Front Biosci (Elite Ed)*, 2, 1184-95 (2010)

78. S. F. Yan, R. Ramasamy and A. M. Schmidt: Soluble RAGE: therapy and biomarker in unraveling the RAGE

axis in chronic disease and aging. *Biochem Pharmacol*, 79(10), 1379-86 (2010)

79. C. Falcone, E. Emanuele, A. D'Angelo, M. P. Buzzi, C. Belvito, M. Cuccia and D. Geroldi: Plasma levels of soluble receptor for advanced glycation end products and coronary artery disease in nondiabetic men. *Arterioscler Thromb Vasc Biol*, 25(5), 1032-7 (2005)

80. D. Geroldi, C. Falcone and E. Emanuele: Soluble receptor for advanced glycation end products: from disease marker to potential therapeutic target. *Curr Med Chem*, 13(17), 1971-8 (2006)

81. F. Santilli, N. Vazzana, L. G. Bucciarelli and G. Davì: Soluble forms of RAGE in human diseases: clinical and therapeutical implications. *Curr Med Chem*, 16(8), 940-52 (2009)

82. E. Leclerc, E. Sturchler, S. W. Vetter and C. W. Heizmann: Crosstalk between calcium, amyloid beta and the receptor for advanced glycation endproducts in Alzheimer's disease. *Rev Neurosci*, 20(2), 95-110 (2009)

83. A. M. Schmidt, B. Sahagan, R. B. Nelson, J. Selmer, R. Rothlein and J. M. Bell: The role of RAGE in amyloid-beta peptide-mediated pathology in Alzheimer's disease. *Curr Opin Investig Drugs,* 10(7), 672-80 (2009)

84. M. O. Chaney, W. B. Stine, T. A. Kokjohn, Y. M. Kuo, C. Esh, A. Rahman, D. C. Luehrs, A. M. Schmidt, D. Stern, S. D. Yan and A. E. Roher: RAGE and amyloid beta interactions: atomic force microscopy and molecular modeling. *Biochim Biophys Acta*, 1741(1-2), 199-205 (2005)

85. E. Emanuele, A. D'Angelo, C. Tomaino, G. Binetti, R. Ghidoni, P. Politi, L. Bernardi, R. Maletta, A. C. Bruni and G. Geroldi: Circulating levels of soluble receptor for advanced glycation end products in Alzheimer disease and vascular dementia. *Arch Neurol*, 62(11), 1734-6 (2005)

86. R. Ghidoni, L. Benussi, M. Glionna, M. Franzoni, D. Geroldi, E. Emanuele and G. Binetti: Decreased plasma levels of soluble receptor for advanced glycation end products in mild cognitive impairment. *J Neural Transm*, 115(7), 1047-50 (2008)

87. K. Li, D. Dai, B. Zhao, L. Yao, S. Yao, B. Wang and Z. Yang: Association between the RAGE G82S polymorphism and Alzheimer's disease. *J Neural Transm*, 117(1), 97-104 (2010)

88. A. Hernanz, M. De la Fuente, M. Navarro and A. Frank: Plasma aminothiol compounds, but not serum tumor necrosis factor receptor II and soluble receptor for advanced glycation end products, are related to the cognitive impairment in Alzheimer's disease and mild cognitive impairment patients. *Neuroimmunomodulation*, 14(3-4), 163-7 (2007)

89. F. Fang, L. F. Lue, S. Yan, H. Xu, J. S. Luddy, D. Chen, D. G. Walker, D. M. Stern, S. Yan, A. M. Schmidt, J. X. Chen and S. S. Yan: RAGE-dependent signaling in microglia contributes to neuroinflammation, Abeta accumulation, and impaired learning/memory in a mouse model of Alzheimer's disease. *FASEB J*, 24(4), 1043-55 (2010)

90. Y. Jang, J. Y. Kim, S. M. Kang, J. S. Kim, J. S. Chae, O. Y. Kim, S. J. Koh, H. C. Lee, C. W. Ahn, Y. D. Song and J. H. Lee: Association of the Gly82Ser polymorphism in the receptor for advanced glycation end products (RAGE) gene with circulating levels of soluble RAGE and inflammatory markers in nondiabetic and nonobese Koreans. *Metabolism,* 56(2), 199-205 (2007)

91. P. Reid and I. Holen: Pathophysiological roles of osteoprotegerin (OPG). *Eur J Cell Biol*, 88(1), 1-17 (2009)

92. P. D'Amelio, G. Isaia and G. C. Isaia: The osteoprotegerin/RANK/RANKL system: a bone key to vascular disease. *J Endocrinol Invest*, 32(4 Suppl), 6-9 (2009)

93. S. M. Venuraju, A. Yerramasu, R. Corder and A. Lahiri: Osteoprotegerin as a predictor of coronary artery disease and cardiovascular mortality and morbidity. *J Am Coll Cardiol*., 55(19), 2049-61 (2010)

94. U. Naumann, W. Wick, R. Beschorner, R. Meyermann and M. Weller: Expression and functional activity of osteoprotegerin in human malignant gliomas. *Acta Neuropathol*, 107(1), 17-22 (2004)

95. L. C. Hofbauer, S. Cepok and B. Hemmer: Osteoprotegerin is highly expressed in the spinal cord and cerebrospinal fluid. *Acta Neuropatho,* 107(6), 575-7 (2004)

96. E. Emanuele, E. Peros, G. A. Scioli, A. D'Angelo, C. Olivieri, L. Montagna and D. Geroldi: Plasma osteoprotegerin as a biochemical marker for vascular dementia and Alzheimer's disease. *Int J Mol Med*, 13(6), 849-53 (2004)

97. A. L. Jefferson, J. M. Massaro, P. A. Wolf, S. Seshadri, R. Au, R. S. Vasan, M. G. Larson, J. B. Meigs, J. F. jr. Keaney, I. Lipinska, S. Kathiresan, E. J. Benjamin and C. DeCarli: Inflammatory biomarkers are associated with total brain volume: the Framingham Heart Study. *Neurology,* 68(13), 1032-8 (2007)

98. C. Luckhaus, B. Mahabadi, B. Grass-Kapanke, M. Jänner, H. Willenberg, M. Jäger, T. Supprian and K. Fehsel: Blood biomarkers of osteoporosis in mild cognitive impairment and Alzheimer's disease. *J Neural Transm*, 116(7), 905-11 (2009)

99. P. Mátyus, B. Dajka-Halász, A. Földi, N. Haider, D. Barlocco and K. Magyar: Semicarbazide-sensitive amine oxidase: current status and perspectives. *Curr Med Chem*, 11(10), 1285-98 (2004)

100. F. Boomsma, P.J. de Kam, G. Tjeerdsma, A.H. van den Meiracker and D.J. van Veldhuisen: Plasma semicarbazide-sensitive amine oxidase (SSAO) is an independent prognostic marker for mortality in chronic heart failure. *Eur Heart J*, 21(22), 1859-63 (2000)

101. M. Unzeta, M. Solé, M. Boada and M. Hernández: Semicarbazide-sensitive amine oxidase (SSAO) and its possible contribution to vascular damage in Alzheimer's disease. *J Neural Transm*, 114(6), 857-62 (2007)

102. Z.J. Jiang, J.S. Richardson and P.H. Yu: The contribution of cerebral vascular semicarbazide-sensitive amine oxidase to cerebral amyloid angiopathy in Alzheimer's disease. *Neuropathol Appl Neurobiol*, 34(2), 194-204 (2008)

103. J.L. Sullivan: Stored iron and vascular reactivity. *Arterioscler Thromb Vasc Biol*, 25, 1532-5 (2005)

104. E.S. Ford: Serum copper concentration and coronary heart disease among US adults. *Am J Epidemiol*, 151(12), 1182-8 (2000)

105. G.J. Brewer: Iron and copper toxicity in diseases of aging, particularly atherosclerosis and Alzheimer's disease. *Exp Biol Med (Maywood)*, 232(2), 323-35 (2007)

106. B. Liu, A. Moloney, S. Meehan, K. Morris, S.E. Thomas, L.C. Serpell, R. Hider, S.J. Marciniak, D.A. Lomas and D.C. Crowther: Iron promotes the toxicity of amyloid {beta} peptide by impeding its ordered aggregation. *J Biol Chem*, 286(6), 4248-56 (2011)

107. S. Bucossi, M. Ventriglia, V. Panetta, C. Salustri, P. Pasqualetti, S. Mariani, M. Siotto, P.M. Rossini and R. Squitti: Copper in Alzheimer's disease: a meta-analysis of serum,plasma, and cerebrospinal fluid studies. *J Alzheimers Dis*, in press (2010)

108. M. Silvestrini, B. Gobbi, P. Pasqualetti, M. Bartolini, R. Baruffaldi, C. Lanciotti, R. Cerqua, C. Altamura, L. Provinciali and F. Vernieri: Carotid atherosclerosis and cognitive decline in patients with Alzheimer's disease. *Neurobiol Aging*, 30(8), 1177-83 (2009)

109. M.J. Jurasic, I.M. Popovic, S. Morovic, Z. Trkanjec, V. Seric and V. Demarin: Can beta stiffness index be proposed as risk factor for dementia. *J Neurol Sci*, 283(1-2), 13-6 (2009)

110. J.C. de la Torre: Is Alzheimer's disease a neurodegenerative or a vascular disorder? Data, dogma, and dialectics. *Lancet Neurol*, 3(3), 184-190 (2004)

111. R.C. Becker: Emerging paradigms, platforms, and unifying themes in biomarker science. *J Am Coll Cardiol,* 50(18), 1777-80 (2007)

112. F. Song, A. Poljak, G. A. Smythe and P. Sachdev: Plasma biomarkers for mild cognitive impairment and Alzheimer's disease. *Brain Res Rev,* 61(2), 69-80 (2009)

113. E. Siemers, R. B. DeMattos, P. C. May and R. A. Dean: Role of biochemical Alzheimer's disease biomarkers as end points in clinical trials. *Biomark Med*, 4(1), 81-9 (2010)

114. P. Schneider, H. Hampel and K. Buerger: Biological marker candidates of Alzheimer's disease in blood, plasma, and serum. CNS Neurosci Ther, 15(4), 358-74 (2009)

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