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Review

Lipid metabolism in cognitive decline and dementia

Francesco Panza[a,*], *Alessia D'Introno*[a], *Anna Maria Colacicco*[a], *Cristiano Capurso*[b], *Gianfranco Pichichero*[a], *Sabrina A. Capurso*[a], *Antonio Capurso*[a], *Vincenzo Solfrizzi*[a]

[a]*Department of Geriatrics, Center for Aging Brain, Memory Unit, University of Bari, Bari, Italy*
[b]*Department of Geriatrics, University of Foggia, Foggia, Italy*

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ABSTRACT

This review will focus on the current knowledge on circulating serum and plasma risk factors of cognitive decline of degenerative (Alzheimer's disease, AD) or vascular origin (vascular dementia, VaD) linked to cholesterol homeostasis and lipoprotein disturbances, i.e. total cholesterol (TC), 24S-hydroxy-cholesterol, lipoprotein(a) (Lp(a)), or apolipoprotein E (APOE). These measures linked to lipoprotein metabolism appear to be altered in AD, VaD, or predementia syndrome relative to controls, but with contrasting results. At present, several studies have demonstrated the dependence of APOE serum levels upon the APOE genotype, nonetheless serum APOE levels seems not to be a credible risk factor or a biochemical marker for AD instead of APOE genotyping. In fact, there was no consistent association of serum or plasma apoE protein levels with the disease when controlled for APOE genotype. In addition, there are some evidence that higher Lp(a) levels could be linked with AD, although there are studies suggesting an increased presence of low molecular weight apo(a) in AD, VaD, and frontotemporal dementia, that are associated with elevated Lp(a) levels. In fact, the apo(a) gene is highly polymorphic in length due to variation in the numbers of a sequence encoding the apo(a) kringle 4 domain, and plasma levels of Lp(a) are inversely correlated with apo(a) size. Furthermore, although serum/plasma levels of TC and 24S-hydroxycholesterol are not credible diagnostic markers for AD and cognitive decline, the current evidence suggests that they may be modifiable risk/protective factors. The prevailing wisdom is that high TC is a risk factor for dementia. However, the relationship between TC and dementia may vary considerably depending on when cholesterol is measured over the life course or, alternatively, in relation to the underlying course of the disease. Several observational studies have suggested that statins, which are effective in lowering cholesterol, may reduce the risk of dementia, but the results of these reports are inconclusive. Thus, more studies with long-term follow-up and serial assessments of TC are needed to further clarify the causal relationship between cholesterol and dementia.

* *Corresponding author*. Fax: +39 080 5478860.
E-mail address: geriat.dot@geriatria.uniba.it (F. Panza).

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Abbreviations:
MCI, mild cognitive impairment
ARCD, age-related cognitive decline
AACD, aging-associated cognitive decline
AD, Alzheimer's disease
VaD, vascular dementia
NFTs, neurofibrillary tangles
SPs, senile plaques
APP, amyloid precursor protein
Aβ, β-amyloid
ILSA, Italian Longitudinal Study on Aging
APOE, apolipoprotein E
CNS, central nervous system
LOAD, late-onset AD
PSEN1, presenilin1
PSEN2, presenilin2
CVD, cerebrovascular disease
LDL-C, low-density lipoprotein cholesterol
HDL-C, high-density lipoprotein cholesterol
CAA, cerebral amyloid angiopathy
Lp(a), lipoprotein(a)
BBB, blood–brain barrier
apo(a), apolipoprotein(a)
FTD, frontotemporal dementia

Contents

1. Introduction

In the next years, the prevalence of cognitive decline and dementia is expected to increase due to prolonged human life expectancy and an increase in the number of elderly people. Epidemiological studies demonstrated an exponential increase in the prevalence of dementia from age 70 to 94, reaching a plateau at 45% at age 95 and older (Wernicke and Reischies, 1994). Still, there are individuals ages 85 and older with no or just very slight cognitive impairment that are at low risk of developing dementia. These results suggest that while dementia is probably age-related, it is not an inevitable consequence of aging. Establishing the diagnosis at the preclinical phase of dementia would be likely to increase the efficacy of treatment.

Mild cognitive impairment (MCI) is, at present, the most widely used term to indicate nondemented aged persons with a mild memory or cognitive impairment that cannot be accounted for any recognized medical or psychiatric condition (Petersen et al., 1999; D'Introno et al., 2004). Different diagnostic criteria have been proposed, and the terms age-related cognitive decline (ARCD) (American Psychiatric Association, 1994) and aging-associated cognitive decline (AACD) (Levy, 1994) have been recently proposed to distinguish individuals with mild cognitive disorders associated with aging from nonaffected individuals. At present, it is difficult to

establish whether these entities are an expression of a normal aging process, or are clinically distinguishable from dementing syndromes, or, eventually, are in a continuum with dementia. In fact, while MCI is assumed to be pathology-based and therefore amenable to interventions, ARCD and AACD are generally considered nonprogressive, a phenomenon of normal aging. Furthermore, MCI may be a prodromal phase of dementia, with estimates of 12% of MCI patients developing dementia in 1 year (Petersen et al., 1999; Panza et al., 2005a), and 20% over 3 years (Petersen et al., 2001). Recently, in the Italian Longitudinal Study on Aging (ILSA), a population-based study with a sample of 5632 65–84 year old subjects, we found a progression rate to dementia of MCI of 3.8/100 person–years (Solfrizzi et al., 2004).

On the other hand, recent studies showed that many people with neuropathological changes of degenerative or vascular origin did not have cognitive impairment (Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study, 2001), also suggesting that MCI could not have a neuropathological basis. In fact, in a sample of nondemented elderly individuals, pathologically confirmed preclinical Alzheimer's disease (AD) was not associated with cognitive impairment or decline, even on neuropsychological measures shown to be sensitive to very mild AD (Goldman et al., 2001). These individuals truly are preclinical in that there is no detectable cognitive deficits despite the presence of neuropathological AD, and detectable cognitive decline already may represent "clinical" AD. In fact, a substantial body of evidence supports the suggestion that MCI largely represents very mild AD (Morris et al., 2001a,b).

Based on current nosology, in occidental countries, the two most common forms of dementia are AD and vascular dementia (VaD), with respective frequencies of 70% and 15% for all dementias (Whitehouse et al., 1997). Therefore, AD is the most common dementia and primary neurodegenerative disorder in the elderly. This neurodegenerative disease gradually leads to a complete psychological and physical dependency and finally to death within one to two decades. It involves aberrant protein processing and is characterized by the presence of both intraneuronal protein clusters composed of paired helical filaments of hyperphosphorilated tau protein [neurofibrillary tangles (NFTs)], and extracellular protein aggregates [senile plaques (SPs)]. The SPs are the result of misprocessing of the amyloid precursor protein (APP) by β- and γ-secretases to form a toxic β-amyloid (Aβ) peptide that aggregates and initiates a pathogenic self-perpetuating cascade ultimately leading to neuronal loss and dementia. According to the "amyloid cascade hypothesis" (Hardy and Higgins, 1992), the development of SPs is thought to precede and precipitate in the formation of NFTs as a result of the cellular changes invoked.

The clinical presentation of VaD varies greatly depending on the causes and location of cerebral damage (Roman, 2002). Large-vessel disease leads commonly to multiple cortical infarcts and a multifocal cortical dementia syndrome, whereas small-vessel disease, usually resulting from hypertension and diabetes, causes periventricular white matter ischemia and lacunar strokes characterized clinically by subcortical dementia with frontal lobe deficits, executive dysfunction, slow information processing, impaired memory, inattention, depressive mood changes, slowing of motor function, Parkinsonian features, small-step gait, urinary disturbances, and pseudobulbar palsy (Roman and Royall, 1999).

It is still not known what causes AD, and specific risk factors for the disease are difficult to isolate. However, since rare mutations that occur in three genes, APP, presenilin1 (PSEN1), and presenilin2 (PSEN2) (Goate et al., 1991; Rogaev et al., 1995; Sherrington et al., 1995), cause familial autosomal-dominant AD with early-onset (less than 5% of all AD cases) and all result in increased production of Aβ, it is clear that this pathway is important. Furthermore, since the remaining 95% of AD cases, predominantly of sporadic and late-onset nature, are neuropathologically indistinguishable from familial forms, it is possible that the disease results from a combination of hereditary and environmental factors that somehow involve the APP pathway. Yet, attempts to identify environmental and genetic risk factors associated with AD have not been conclusive. The risk factors identified so far are intriguing but not completely illuminating.

Numerous genes related to vascular disease have been shown to increase susceptibility for sporadic AD (Panza et al., 2004a). Among these genetic risk factors, apolipoprotein E (APOE) which is located on chromosome 19 and occurs in three common alleles, ε2, ε3, and ε4, is the best-documented one. In fact, the APOE e4 allele is a major risk factor for getting sporadic AD. The APOE protein is one of the major constituents in very low-density lipoproteins and plays a key role in the transport of cholesterol and other lipids among various cells of the body. The importance of APOE in the central nervous system (CNS) became evident with the association of the ε4 allele of APOE with familial and sporadic LOAD (Saunders et al., 1993). The APOE ε4 allele has been known to be associated with coronary artery disease (CAD), and the development of atherosclerosis well before its association with AD (Davignon et al., 1988). The association with CAD is presumably related to the higher levels of TC, low-density lipoprotein cholesterol (LDL-C), and apolipoprotein B in subjects homozygous for the APOE ε4 genotype than in those ε2- or ε3-carriers. This fact that APOE is neither necessary nor sufficient to cause AD is the main reason why APOE is classified as a risk factor for an AD and not a causative one. Furthermore, APOE genotyping predictive value is poor and it is not very sensitive and specific, and this is the main case used to argue against proposals for the inclusion of APOE genotyping in clinical diagnoses of AD. Thus, APOE testing can be performed only in patients suspected of having AD, but not in healthy people or relatives of AD patients as screening or predictive test (American College of Medical Genetics/American Society of Human Genetics Working Group on ApoE and Alzheimer disease, 1995). For a person with symptoms of dementia, APOE testing may offer additional support that any dementia may be due to AD, and thus potentially increase confidence to the clinical diagnosis (Mayeux et al., 1998). In AD Centers, clinical diagnosis is already deemed to be correct over 90% of the time without any APOE testing. When APOE genotyping is performed in combination with the clinical criteria for the

disease, the specificity of the diagnosis is increased by an estimated additional 4%.

The degenerative process in AD has already progressed to an advanced stage with massive loss of cell mass before diagnosis can be made. The transition from normal cognitive performance to the AD phenotype is probably gradual, with MCI patients prone to develop AD (Jack et al., 2000). Considering the limited capacity of the CNS tissue to repair, early intervention in the degenerative processes, thus in patients with MCI, will be crucial to spare as much tissue as possible. Early diagnosis may then help to increase the possibilities for developing and testing new preventive strategies (Panza et al., 2005b).

This review will focus on the current knowledge on circulating serum and plasma risk factors of cognitive decline of degenerative or vascular origin, linked to cholesterol homeostasis and lipoprotein abnormalities. We reviewed clinical and epidemiological studies from the international literature through keyword and author searches in Medline from January 1981 to May 2005.

2. Risk factors related to lipoprotein metabolism and vascular disease

While one of the most popular theories for the pathogenesis of late-onset AD (LOAD) remains the "amyloid hypothesis", another exciting area is rapidly developing around vascular risk factors as a key part of AD pathology (Panza et al., 2004b). This relationship between risk factors for vascular disease and AD appears at first glance contradictory, since vascular risk factors and the presence of cerebrovascular disease (CVD) have been considered as exclusion criteria for the clinical diagnosis of AD. Furthermore, for a number of years, epidemiological studies have considered that the cooccurrence of various forms of vascular disease and dementia has been coincidental and largely dependent on the fact they are both common disorders. However, more recently, these cooccurences, although unexplained as yet, are thought have a more pathological significance (Kehoe, 2003). In fact, recent studies suggest that microvascular disorder may contribute to AD pathogenesis and synergistically to cognitive decline related to AD pathology (Farkas and Luiten, 2001), but the role of cerebrovascular pathology in AD is a matter of controversy (Kalaria, 2000; Skoog, 2000; Wakutani et al., 2002). Vascular pathology of the aging brain and AD includes cerebral amyloid angiopathy (CAA), causing lobar mass hemorrhages, small or recurrent bleeds and ischemic infarcts, microvascular degeneration, disorder of the blood–brain barrier (BBB), white matter lesions, microinfarctions, lacunes, and cerebral hemorrhages (Jellinger, 2002). Furthermore, many of the risk factors for CVD and VaD, including circulating factors such as serum/plasma total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), lipoprotein(a) [Lp(a)], and serum APOE levels, or vascular-related diseases such as diabetes mellitus, atrial fibrillation, hypertension, and atherosclerosis, have also been shown to increase the risk of AD. The degree to which these risk factors contribute to cognitive decline may be influenced by genetic factors, such as APOE, that have a role in both vascular disorders and AD (Wakutani et al., 2002; Panza et al., 2004a).

Recent evidence from population-based studies (Di Carlo et al., 2000; Kivipelto et al., 2001a; DeCarli et al., 2001; Lopez et al., 2003) and case series (Frisoni et al., 2002; DeCarli et al., 2004) suggests that CVD and vascular factors may contribute to the heterogeneity of MCI. In fact, as seen above, factors, such as hypertension, smoking, diabetes mellitus, atrial fibrillation, and the APOE ε4 allele are also associated with late-life cognitive decline (Panza et al., 2004b), and so may influence the development of MCI and dementia. Because such vascular factors may be modifiable, identification and subsequent management of these possible risk factors may help to prevent and reduce conversion rates of MCI and dementia. In a recent study, we estimated prevalence, incidence, and rate of progression of MCI to dementia and correlated vascular risk factors with incident MCI and its progression to dementia (Solfrizzi et al., 2004). During the 3.5-year follow-up, 113 new events of MCI were diagnosed with an estimated incidence rate of 21.5 per 1000 person–years. We found a progression rate to dementia (all causes) of 3.8/100 person–years. Furthermore, age was a risk factor for incident MCI, while education was protective, and serum TC evidenced a borderline nonsignificant trend for a protective effect. Furthermore, there was a nonsignificant trend for stroke as a risk factor of progression of MCI to dementia. Probably, a follow-up period longer than 3.5 years would reveal that other vascular factors could influence the progression of MCI to dementia. In conclusion, in our population, among those who progressed from MCI to dementia, 60% progressed to AD and 33% to VaD. Vascular risk factors may influence incident MCI and the rate of progression to dementia. Furthermore, our findings on the role of stroke in the progression of MCI patients to dementia in the ILSA sample (Solfrizzi et al., 2004), in conjunction with previous studies (Vermeer et al., 2003), suggest that stroke and CVD play a role in the clinical course of preclinical dementia. This may indicate new options for prevention of dementia that include CVD and stroke prevention (Panza et al., in press).

3. Total and low-density lipoprotein cholesterol and cognitive decline

Cholesterol is the main lipid constituent of neuronal membranes and myelin (Dietschy and Turley, 2001). It is known that cholesterol is synthesized in the brain in situ (Dietschy and Turley, 2001) and that extracerebral cholesterol does not contribute significantly to brain cholesterol content (Jurevics and Morell, 1995). Excess of brain cholesterol has to be removed into the periphery. The mechanism of transport is unclear, but may be mediated by APOE and by facilitated transport of oxidized products like 24S-hydroxycholesterol (Lutjohann et al., 1996). However an, additional, as yet unknown, transport mechanism may be involved (Dietschy and Turley, 2001). It has been hypothesized that during neurodegenerative processes an increased removal of cholesterol from the brain occurs (Bjorkhem et al., 1998). Aberration of cholesterol homeostasis may indeed be involved in AD (Poirier, 2005). In fact, several experimental studies have reported that modification of cholesterol content can

influence the expression of the APP and Aβ (Bodovitz and Klein, 1996; Howland et al., 1998; Mizuno et al., 1998, 1999; Ross et al., 1998; Simons et al., 1998; Kojro et al., 2001; Fassbender et al., 2001; Wahrle et al., 2002). For example, a decreased level of brain cholesterol led to a reversible decreased formation of Aβ in cultured hippocampal neurones (Simons et al., 1998). A recent paper reported that cholesterol accumulated in SPs of AD patients and 24 months old transgenic mice that overexpress APP (Tg APPsw) (Mori et al., 2001). In addition, the unesterified cholesterol to phospholipid ratio was decreased in the temporal gyrus of AD patients, while the TC concentration was unchanged (Mason et al., 1992). In some studies (Merched et al., 2000; Siest et al., 2000), decreased serum TC and high-density lipoprotein cholesterol (HDL-C) concentration in AD patients was observed compared to controls, whereas others observed increased TC and LDL-C in AD patients (Bonarek et al., 2000; Reitz et al., 2004).

Other evidence includes the effect of diet on Aβ pathology in animals (Sparks et al., 1994; Refolo et al., 2001). Administration of diets high in cholesterol increased Aβ accumulation in brain tissue of transgenic mice overexpressing APP and presenilin-1 as compared with transgenic controls (Refolo et al., 2000). There was a small but significant increase (1.92 mg/g) in cholesterol in brain tissue of mice fed the high cholesterol diets. As seen above, lipids are essential for the structural and functional integrity of membranes. Membrane lipids are not randomly distributed but are localized in different domains. These domains consist of the exofacial and cytofacial leaflets, cholesterol pools, annular lipids, and lipid rafts. Recent data reveal the very interesting possibility that membrane lipid domains may be a target of AD (Wood et al., 2002). It was suggested in the study by Refolo et al. (2000) that brain lipid domains could be affected by the high cholesterol diet. Large changes in brain lipid domains, particularly cholesterol domains, could occur without major alteration in the total amount of cholesterol.

There is certainly an association between cholesterol and AD. However, it remains to be determined if cholesterol synthesis and metabolism are altered in brains of AD patients or animal models of AD. Data are equivocal for example on total or bulk cholesterol content in brain tissue of AD patients and studies with animal models of AD show little if any changes in cholesterol content. An alternative approach in contrast to changes in bulk cholesterol is that modification of the structure or function of neuronal membrane cholesterol domains plays a major role in AD by acting on Aβ dynamics (Wood et al., 1999; Eckert et al., 2000; Refolo et al., 2000).

Epidemiological studies showed that the onset of AD occurs earlier in APOE ε4-carriers with high serum TC (Jarvik et al., 1995). Moreover, high serum TC during middle age or early old age seems to confer an increased risk of AD in older age (Notkola et al., 1998). In fact, a recent population-based prospective study with a 21-year follow-up in Finland found that high TC levels in middle age were associated with increased risk of AD in later life (Kuusisto et al., 1997). However, even if high TC often clusters with hypertension, these two entities seem to be independent risk factors of AD (Kivipelto et al., 2001a). Furthermore, high cholesterol levels were associated with an increased risk of AD or cognitive impairment in cross-sectional and prospective studies (Evans et al., 2000; Yaffe et al., 2002). On the contrary, our findings on lower TC serum levels in AD (Solfrizzi et al., 2002) confirmed the data of cross-sectional and prospective studies in which a weak but significant inverse association with AD was found, independently of APOE genotype (Kuusisto et al., 1997; Romas et al., 1999). Furthermore, the Hisayama study found no association between serum TC and AD over a 7-year follow-up (Fujishima and Kiyohara, 2002), and no association was found in the Framingham cohort (Tan et al., 2003). These findings were confirmed by another study that found no difference in serum TC or hyperlipidemia between subjects with AD, VaD, or nondemented subjects (Boston et al., 1999) and by the Honolulu–Asia Aging Study (Kalmijn et al., 2000). In fact, in this prospective population-based study among Japanese–American men, a higher cardiovascular metabolic risk factor burden in middle age increased the risk of dementia 25 years later, clustering 7 vascular risk factors (random postload glucose, diastolic and systolic blood pressures, body mass index, subscapular skinfold thickness, random triglycerides, and TC). Nonetheless, the metabolic cardiovascular syndrome particularly increased the risk of VaD, not AD and after adjustment for age and education, an increase of 1 standard deviation of body mass index, skinfold thickness, and triglyceride levels increased the risk of dementia. None of these individual risk factors was associated with AD, and all of the vascular risk factors, except TC and triglyceride levels, were positively and significantly associated with VaD. A few studies have investigated the influence of APOE genotype on the relationship between plasma lipid level and dementia risk, and they have given conflicting results (Notkola et al., 1998; Romas et al., 1999; Evans et al., 2000; Kivipelto et al., 2002). Nonetheless, TC levels may be influenced by APOE genotype, sex, age, and stage of AD (Notkola et al., 1998; Evans et al., 2000).

Very recently, Mielke et al. (2005) examined the association between cholesterol level and dementia in a population-based 70-year-old birth cohort followed for 18 years. Increasing TC levels at ages 70, 75, and 79 were associated with a reduced risk of dementia between ages 79 and 88. In this 18-year longitudinal study of 70 year olds, examination of cholesterol in quartiles showed that the reduction in risk was associated exclusively with the highest quartile. The exclusion of lipid-lowering medication users did not attenuate the association. Furthermore, the association was found only among non-smokers, and no association between triglyceride levels and dementia was reported. Therefore, high TC in late life was associated with decreased dementia risk, which is in contrast to previous studies suggesting that high cholesterol in midlife is a risk factor for later dementia (Kuusisto et al., 1997; Notkola et al., 1998). The conflicting results may be explained by the timing of TC measurements in relationship to age and the clinical onset of dementia (Mielke et al., 2005). This has been suggested for blood pressure and body mass index (BMI) studies with more than 10 years of follow-up (Skoog et al., 1996; Launer et al., 2000; Gustafson et al., 2003), high blood pressure and BMI have been associated with an increased risk of AD. However, in studies with less than 10 years of follow-up (Li et al., 1992; Barrett-Connor et al., 1996; Tsolaki et al., 1997; Morris et al., 2001a,b), the null or opposite relationship has been observed. The divergent findings appear to be due to the

Table 1 – Principal population-based and case–control studies on plasma and serum total cholesterol levels in Alzheimer's disease (AD), other dementigen disorders, and mild cognitive impairment

Reference	Subjects	Diagnosis	Results
Jarvik et al. (1995)	206 cases 276 controls	AD	The onset of AD occurs earlier in APOE ε4-carriers with high serum TC
Kuusisto et al. (1997)	980 people aged 69 to 78 years (349 men, 631 women) from population-register of Kuopio, eastern Finland; 46 (4.7%) AD cases	AD	Lower serum TC was associated with an increased risk for AD in older age, independently of apoE genotype
Notkola et al. (1998)	444 men, aged 70–89 years, who were survivors of the Finnish cohorts of the Seven Countries Study	AD	High serum TC during middle age or early old age seems to confer an increased risk of AD in older age
Boston et al. (1999)	222 AD cases 34 VaD cases 140 nondemented	AD VaD	No difference in TC levels by diagnosis
Romas et al. (1999)	1449 white, African–American, and Caribbean Hispanic subjects from population-register from New York City, aged 75.8 + 6.4 years	Incident AD	Decreased plasma TC level had an inverse association with incident AD, independently of APOE genotype
Evans et al. (2000)	524 African–Americans subjects older than from 65 years from door-to-door random sampling	AD	Increasing TC was associated with increased AD risk in the group with no APOE ε4 alleles, whereas TC was not associated with increased AD risk in the group with one or more ε4 alleles
Kivipelto et al. (2001a)	1449 subjects aged from 65 to 79 years	Incident AD	Midlife high serum TC and raised systolic blood pressure, and in particular the combination of these risks, increased the risk of AD in later life
Bonarek et al. (2000)	Nested case–control study of 334 elderly French subjects aged 73 and over who participated in the PAQUID study; 37 dementia cases, 297 nondemented	Dementia	No difference in TC levels by diagnosis. Elevated HDL-C was associated with a significantly decreased risk of dementia, independently of APOE status
Kalmijn et al. (2000)	Of the 4678 men from 71 to 93 years of the original cohort of 8006 Japanese–American, 3734 (80%) participated in the dementia case-finding effort	Incident dementia, incident AD, and incident VaD	After adjustment for age and education, body mass index, skinfold thickness, and triglyceride levels increased the risk of dementia. TC and triglyceride levels were not associated with AD or VaD
Kivipelto et al. (2001b)	50 definite AD cases 27 probable AD cases 50 possible AD cases 22 no AD subjects	Incident MCI	Midlife elevated serum TC level (> or = 6.5 mmol/L) was a significant risk factor for MCI
Kivipelto et al. (2002)	1449 subjects aged from 65 to 79 years	Incident AD	Midlife high serum TC and raised systolic blood pressure were independent risk factors for AD in later life, independently of APOE status
Solfrizzi et al. (2002)	61 cases 63 controls	AD	Lower serum TC in AD patients Lipoprotein (a) serum concentrations were significantly associated with an increased risk for AD, independently of APOE genotypes and sex and dependent on age and TC serum concentrations
Tan et al. (2003)	1026 subjects from the Framingham Study original cohort, aged 78.1 + 5.3 years	Incident AD	Serum TC levels were not associated with the risk for incident AD
Reitz et al. (2004)	4316 Medicare recipients,	AD and VaD	Elevated levels of non-HDL-C and

Table 1 (*continued*)

Reference	Subjects	Diagnosis	Results
	65 years and older, residing in northern Manhattan, New York	Incident AD and VaD	LDL-C and decreased levels of HDL-C were weak risk factors for VaD in either cross-sectional or prospective analyses Higher levels of TC were associated with a decreased risk of incident AD after adjustment for demographics, APOE genotype, and cardiovascular risk factors
Solfrizzi et al. (2004)	2963 Italian subjects from population-register (including institutions) aged from 65 to 84 years	Incident MCI	Serum TC evidenced a borderline nonsignificant trend for a protective effect
Dufouil et al. (2005)	A population-based cohort of 9294 subjects selected from the electoral rolls of three French cities (Bordeaux, Dijon, Montpellier)	Incident dementia, incident AD, and incident VaD	Higher TC (> = 6.20 mmol/L) was associated with an increased odds of dementia but not AD
Mielke et al. (2005)	A total of 392 individuals, 166 men and 226 women, from the 70-year-old residents of Göteborg in 1971 to 1972	Incident dementia	In this 18-year longitudinal study of 70 year olds, an association between higher TC and a decreased risk of dementia was observed

AD: Alzheimer's disease.
TC: total cholesterol.
APOE: apolipoprotein E.
VaD: vascular dementia.
HDL-C: high-density lipoprotein cholesterol.
LDL-C: low-density lipoprotein cholesterol.
MCI: mild cognitive impairment.

fact that several years before dementia, onset blood pressure and BMI begin to decline, possibly as a result of the ongoing AD pathology, suggesting that the same may be true for TC.

In a retrospective study conducted on autopsy cases of patients older than 40 years, mild elevation in TC may be an early risk factor for the development of Alzheimer amyloid pathology in the human brain, with a significant association between plasma TC level and presence of amyloid deposition. Although a significant association was retained in the whole sample, it was interesting that no association between TC and amyloid deposition occurred at older ages (>55 years) (Pappolla et al., 2003). The calculated odds for developing amyloid almost tripled with only a 10% increase in TC level in the younger group. These findings may also explain the lack of consensus regarding the association between TC and AD, suggesting that only midlife elevation in TC may be a risk factor for AD. On the other hand, recent findings from the Framingham Study showed that participants with "desirable" TC levels (<200 mg/dL) performed less well than participants with borderline-high TC levels (200–239 mg/dL) and participants with high TC levels (1240 mg/dL) on cognitive measures of verbal fluency, attention/concentration, abstract reasoning, and a composite score measuring multiple cognitive domains (Elias et al., 2005).

Our findings on lower TC serum levels in AD (Solfrizzi et al., 2002) were confirmed from data of the ILSA, in which the multivariable analysis suggested that only age was a risk factor for incident MCI, while higher levels of education and serum TC appeared to have a protective effect (Solfrizzi et al., 2004). On the contrary, Kivipelto et al. (2001b) found that midlife elevated TC serum levels (>6.5 mmol/L) increased the risk for MCI (OR: 1.9), with systolic blood pressure showing a similar trend. In addition, DeCarli et al. (2001) showed that elevated midlife blood pressure increased the risk for MCI. We did not confirm that elevated TC is a risk factor for incident MCI (Solfrizzi et al., 2004). This discrepancy can be explained by the fact that both TC and blood pressure were midlife determinations (with average follow-up of 21 and 25 years) in the Kivipelto et al. (2001b) and DeCarli et al. (2001) studies, respectively (Table 1).

Therefore, it is possible that high TC plays a role in protecting against dementia and MCI. Experimental studies suggest that high cholesterol accelerates the production of Aβ in AD, by shifting APP metabolism from alpha to beta cleavage products (Sparks et al., 1994; Simons et al., 1998). It seems unlikely that the mechanism associated to protection against cognitive decline involves the amyloid cascade. Perhaps cholesterol supports other elements of neural integrity. In fact, cholesterol is an essential molecule for many physiologic processes and may have several beneficial effects as well. Cholesterol is a precursor of steroid hormones (estrogens, androgens, vitamin D), provides structural integrity and modulates fluidity of cell membranes, and is essential for basic synaptic integrity and neurotransmission (Oliver, 1981; Koudinov and Koudinova, 2001). All these processes are compromised with aging and have been shown to be dysfunctional in patients with AD. In addition, in vitro studies have suggested that cholesterol acts as an antioxidant and

therefore has a protective role in dementia pathogenesis (Vatassery et al., 1995; Joseph et al., 1997), possibly through intercepting pro-oxidants to create oxysterols, which are less toxic than free radicals. Alternatively, TC may be lowered by some aspect of the incipient dementing process, such as decreasing nutrition, years before onset of symptoms: cholesterol lowering might be an effect rather than a cause of dementia. The fact that relatively lower cholesterol at age 70 precedes the onset of dementia does not mean that lipid-lowering treatment should be withheld from middle-aged individuals.

4. Lipid-lowering treatment and dementia

Circulating lipoproteins and lipids can be modified by dietary or pharmacologic intervention and TC is an established marker of the effects of lipid-lowering treatment. Some epidemiological studies also indicate that the prevalence of AD might be decreased in patients treated with the 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCoAr) inhibitors (statins) (Crisby et al., 2002). The relative risk of dementia in statin users was 0.21–0.29 in case–control studies from the United Kingdom and Canada (Jick et al., 2000; Rockwood et al., 2002). This last evidence from a recent longitudinal observation from the Canadian Study of Health and Aging (CSHA) (Rockwood et al., 2002) that incidence of AD was reduced in individuals using statins further supports the hypothesis that TC may be important in AD. Moreover, one observational study in three hospitals in the United States recently found that the prevalence of AD among patients taking statin drug was 60–73% lower than in patients not on statins (Wolozin et al., 2000).

Some statins such as lovastatin, simvastatin, and cerivastatin (no longer available in US and Italy) are able to cross the BBB into the CNS, while others such as atorvastatin, pravastatin, rosuvastatin, and fluvastatin do not (Knopp, 1999).These statins are thought to reduce the amount of Aβ peptides by reducing cholesterol from the blood and/or the CSF (Bales et al., 1997). By reducing the amount of Aβ peptides, they may reduce the incidence or the progression of AD. Some believe statins which do not cross the BBB should be preferred as those that cross the BBB may increase the rate of neuronal death by decreasing cholesterol beyond what is needed for neuronal formation (Sparks et al., 2002). Moreover, statins show pleiotropic effects including regulation of eNOS activity and NO production, modulation and inflammatory processes, antioxidant activity, angiogenesis, and immunomodulation, as well as reduction of free TC and inhibition of cholesterol ester accumulation in macrophages by inhibiting LDL endocytosis and reducing mevalonate byproducts essential for cholesterol esterification. Other potential effects of statins include reduction of atherosclerotic plaque formation, endothelial protection, and reduction of oxidized LDL (Jick et al., 2000).

This association is significant regardless of other risk factors for dementia and suggests that statins may prevent dementia, a possibility that requires confirmation by adequate randomized controlled studies. Most clinical trials of statins have evaluated only the cardio- and cerebrovascular effects of this treatment in middle-aged persons (Panza et al., in press). A recent trial assessing the benefits of pravastatin in individuals ages 70 to 82 years, at high risk of cardiovascular disease and stroke, did not find any significant effect of this lipid-lowering agent on cognitive performance (Shepherd et al., 2002). However, no effect on a secondary measure of incident cognitive decline occurred in a placebo-controlled study of simvastatin for cardiac disease involving 20,536 patients, despite a prominent lipid-lowering benefit (Heart Protection Study Collaborative Group, 2002). Furthermore, in a prospective, cohort study of statin use and incident dementia and probable AD with a cohort of 2356 cognitively intact persons, aged 65 and older, employing time-dependent proportional hazards modeling, the authors found no significant association between statin use and incident dementia or probable AD (Li et al., 2004). In contrast, when the data were analyzed, inappropriately, as a case–control study, the authors found an OR of 0.55 for probable AD, falsely indicating a protective effect of statins. Therefore, study design and analytic methods may explain the discrepancy between the current null findings (Li et al., 2004) and earlier findings (Wolozin et al., 2000; Heart Protection Study Collaborative Group, 2002; Rockwood et al., 2002).

Very recently, the Three-City Study, a large community-based cohort of 9294 subjects ages 65 years and older selected from the electoral rolls of three French cities (Bordeaux, Dijon, Montpellier), examined whether lipid-lowering drug use (statins and fibrates) and hyperlipidemia were associated with prevalence of dementia and, if so, if the association was modified by variants in the APOE genotype (Dufouil et al., 2005). The analyses suggested that use of lipid-lowering drugs was associated with a lower prevalence of dementia. This trend was consistently found in subgroup analyses by age, gender, and center and for both statins and fibrates. It was also found when the analysis was restricted to AD cases, with no modifying effect of the APOE genotype on the association between lipid-lowering drug use and dementia. Moreover, when TC level and lipid-lowering drug intake were studied concomitantly, an association between lipid-lowering drug use and lower prevalence of dementia was found only in lipid-lowering agent users with normal TC level (Dufouil et al., 2005). High TC levels were related to higher dementia prevalence but only in non-AD cases, as already observed in another study (Reitz et al., 2004) (Table 1). In fact, this very recent cross-sectional and prospective community-based cohort study found a weak relation between non-HDL-C, LDL-C, and HDL-C levels and the risk of VaD. Lipid levels and the use of agents to lower them do not seem to be associated with the risk of AD (Reitz et al., 2004). These recent findings confirmed previous data showing that elevated levels of LDL-C were associated with the risk of dementia with stroke in elderly patients (Moroney et al., 1999).

Studies that have investigated the relationship between lipid-lowering drugs and dementia have been based on a solid rationale (Wolozin, 2004). It is well established that the risk of AD and cognitive impairment is increased in patients with pathologic conditions associated with high TC levels, such as cardiovascular disease and carotid atherosclerosis (Aupérin et al., 1996; Carmelli et al., 1998; Hofman et al., 1997). As seen above, laboratory studies have further shown that cholesterol

might play a role in the biosynthesis of Aβ (Frears et al., 1999), and that simvastatin reduces the level of Aβ42 and Aβ40 in the brain of guinea pigs (Fassbender et al., 2001). However, the findings from epidemiologic studies investigating the association between TC levels and dementia are inconclusive. Only a few of these studies, however, has taken into account lipid-lowering drug intake, which limits their interpretation. These reports follow-up a series of independent animal and cellular studies that examined the cholesterol/amyloid metabolic interaction in the context of cell survival and toxicity. While these studies clearly implicate the role of cholesterol in Aβ processing and vice versa, little is known regarding the exact contribution of the cholesterol synthesis pathway, particularly the HMGCoAr enzyme, in this molecular cascade.

Analysis of HMGCoAr activity in the brains of autopsy-confirmed AD cases revealed a marked reduction in the activity of this enzyme in cortical and hippocampal areas, when compared with age-matched control subjects (Poirier, 2002). This reduction in HMGCoAr enzymatic activity was found to be APOE-genotype-independent. The HMGCoAr gene locus is only a few centimorgans away from a polymorphic DNA marker on chromosome 5 that is associated with late-onset familial AD (Kehoe et al., 1999). Although no difference was observed between HMGCoAr mRNA levels in AD versus control subjects (Yasojima et al., 2001; Poirier, 2002), an abnormal transcript containing intron M of the gene was detected in nearly all the AD subjects examined (13). A loss of HMGCoAr activity would certainly be consistent with the reduced cholesterol levels in brain regions affected by AD pathology (Mulder et al., 1998; Poirier, 2002). The statin observations are also consistent with a previous work on probucol, the first generation of cholesterol lowering agents, which was used in the mid-80s to treat familial hypercholesterolemia and to reverse skin cholesterol deposition. In a 6-month clinical investigation, the effect of a standard dose of probucol in mild-to-moderate AD was examined. The pilot study revealed concomitant stabilization of the AD symptoms on cognitive and functional scales, and a significant induction of the APOE levels in the CSF of these patients (Poirier, 2003; Poirier and Panisset, 2002). A significant inverse relationship between the increase CSF APOE levels and the reduction of total CSF Aβ levels was also observed in the brain probucol-treated AD subjects (Poirier, 2003).

Recent results obtained in prospective clinical studies with statin in AD subjects are, however, much less conclusive. It has been reported that statins do not affect or slightly reduce plasma or CSF amyloid concentrations (Fassbender et al., 2002; Tokuda et al., 2001). Simvastatin has been evaluated in two studies (Sjogren et al., 2003; Simons et al., 2002). In one study of 19 patients, after 12 weeks of simvastatin 20 mg/day, serum concentrations of cholesterol and LDL and CSF concentrations of a-sAPP and b-sAPP decreased. As there was no placebo group, the significance of these results cannot be determined. Simons et al. (2002) performed a randomized double-blind placebo-controlled trial of simvastatin 80 mg/day for 26 weeks in 44 patients with AD. CSF lathosterol and 24S-hydroxycholesterol, and serum LDL were significantly decreased compared with placebo. Two other studies have evaluated the effects of statins on Aβ peptides in the human population. Ishii et al. (2003) studied pravastatin 10 mg/day for at least 3 months in 46 hyperlipidemic patients without AD and found that plasma concentrations of Aβ40 and Aβ42 did not decrease. Another study showed that doses of 40 and 60 mg/day of controlled release lovastatin produced a dose-dependent decrease in serum Aβ, with levels different from placebo (Buxbaum et al., 2002).

At present, there is insufficient evidence to show that statins reduce the progression of AD. Statins decrease certain surrogate markers but their influence in decreasing the progression of AD is unknown (Caballero and Nahata, 2004). The clinical retrospective benefits are difficult to interpret as no large double blind placebo-controlled clinical trials have been completed at this point time. The preclinical work done in normal mice, APP mice, or guinea pig while intriguing, refers to concentration of statins that are several orders of magnitude higher than what is widely accepted for human use. Overall, these preliminary results indicate that modulation of brain cholesterol homeostasis may interfere with disease onset and/or progression in subjects exposed to lipid-lowering agents prior to, or following a diagnosis of AD. Alternatively, low concentration of statins could penetrate the BBB and target HMGCoAr in specific cell types such as neurons, to reduce intracellular cholesterol levels, and upregulate the LDL receptor protein family. Finally, it would caused a massive influx of cholesterol-rich APOE-lipoproteins, induction of synaptic remodeling and terminal proliferation. While it remains difficult to determine the exact mechanism of action by which lipid-lowering agents affect the pathophysiology of AD, the recent finding of abnormal forms of the HMGCoAr in the brain of AD subjects (Poirier, 2002) provides us with an intriguing new explanation or the molecular basis of this protective effect in common sporadic AD.

Controlled trials have confirmed a link between vascular factors and dementia described in several epidemiological studies (Skoog, 1997; Forette et al., 2002). So far, trials assessing the benefit of lipid-lowering drugs, more specifically statins, on cognition have been conducted in patients at high vascular risk and have failed to demonstrate a significant treatment effect (Heart Protection Study Collaborative Group, 2002; Shepherd et al., 2002). One explanation for this discrepancy between observational and controlled studies could be that statins have multiple effects. Statins might protect cognitive function through an effect on neurodegenerative rather than ischemic cerebral lesions. Until now, it has been suggested, for example, that statins and probucol might influence Aβ production (Vaughan et al., 1997; Petanceska et al., 2002; Crisby et al., 2002; Champagne et al., 2003). Other mechanisms that have been proposed to explain the effect of statins on the risk and the severity of stroke might also be involved in their cognitive effects: increase in endothelial nitrous oxide synthase and anti-inflammatory and neuroprotective effects (Kirsch et al., 2003; Gibson et al., 2003). Nonetheless, the Three-City Study suggests that lipid-lowering drug use is associated with a reduced risk of dementia only in subjects who had normal lipid levels (Dufouil et al., 2005). This is rather in favor of a putative effect of lipid-lowering agents that is related to lipid-lowering properties. But this could reflect as well that people who do not respond to lipid-lowering treatment are at higher risk for dementia or that subjects who take lipid-

lowering agents and still have high TC levels had higher TC levels at baseline.

5. 24S-hydroxycholesterol in AD and MCI

As seen above, plasma 24S-hydroxycholesterol reflects brain cholesterol homeostasis more closely than plasma TC. Excess brain cholesterol is converted to 24S-hydroxycholesterol, a brain-specific oxysterol which readily crosses the BBB (Lutjohann et al., 1996). In fact, there is a daily flux of about 7 mg of this oxysterol from the brain to the circulation, with the majority of this efflux apparently occurring as direct transport across the BBB (Bjorkhem et al., 1998). 24S-hydroxycholesterol levels in plasma represent a balance between production in the brain and metabolism in the liver. Plasma levels show a weak, if any, correlation with CSF levels (Papassotiropoulos et al., 2002). 24S-hydroxycholesterol was elevated in the CSF of AD and MCI patients (Papassotiropoulos et al., 2002; Schonknecht et al., 2002). Therefore, the elevation of 24S-hydroxycholesterol appears to occur early in the disease process, suggesting that CSF 24S-hydroxycholesterol may be a marker for monitoring the onset and progression of the disease (Schonknecht et al., 2002). On the contrary, the findings on a possible elevation also in plasma of 24S-hydroxycholesterol in AD and VaD patients were contrasting (Lutjohann et al., 2000; Bretillon et al., 2000; Schonknecht et al., 2002; Leoni et al., 2003) and plasma 24S-hydroxycholesterol levels were reduced by statin and niacin treatment (Simons et al., 2002; Locatelli et al., 2002; Vega et al., 2003). 27-hydroxycholesterol is the most abundant hydroxycholesterol in human circulation (Dzeletovic et al., 1995). The recently published observation of a strong correlation between 24S- and 27-hydroxycholesterol CSF levels (Leoni et al., 2003) suggested that not only brain oxysterols such as 24S-hydroxycholesterol are altered in dementing disorders, but that also peripheral cholesterol metabolism is affected. These suggestions are supported by the recent findings of increased ratios of plasma 24S-hydroxycholesterol to 27-hydroxycholesterol in patients with dementing disorders compared to nondemented subjects (Kolsch et al., 2004). In conclusion, although serum/plasma levels of TC, LDL-C, and 24S-hydroxycholesterol are not credible diagnostic markers for AD and cognitive decline, at present, the current evidence suggests that they may be modifiable risk/protective factors.

6. Possible role of lipoprotein(a) in dementing disorders

Lipoprotein(a) (Lp(a)) is a LDL-like particle with the plasminogen-like apolipoprotein(a) (apo(a)) linked by disulfide bridge to apolipoprotein B-100, that is believed to have atherogenic and thrombotic properties and has been associated with vascular disease (Marcovina et al., 2003). In fact, high Lp(a) levels are associated with atherosclerosis, CAD, and CVD (Milionis et al., 2000). Unlike all other lipoproteins, plasma Lp(a) concentration is mainly determined by genetic factors at the apo(a) gene or other sequences located either within or near the apo(a) locus. In fact, the apo(a) gene is highly polymorphic in size as a result of differences in the number of repeated kringle 4 (K4) units in apo(a) (Marcovina et al., 2003). Analysis of the molecular weight (MW) of apo(a) by denaturing electrophoresis reveals heterogeneity or isoforms. State-of-the-art phenotyping separates over 30 different isoforms of apo(a) that vary in the number of repeats of K4 (Marcovina et al., 2003). Indeed, it has been shown that the majority of Lp(a) cell-to-cell interactions are mediated by its specific apo(a) moiety, and plasma levels of Lp(a) are inversely correlated with apo(a) size (Kamboh et al., 1994). Studies of DNA separated the genetic determinants of Lp(a) into the "*cis*-acting" elements and the protein polymorphism. In Caucasians, 90% of the concentration is genetically determined, with about 50% contributed by the *cis*-acting elements and about 40% contributed by the number of K4 repeats (Puckey et al., 1997). It is clear that, if the protein polymorphism codes for a very high MW isoform, then Lp(a) concentration is always very low, whereas if the protein polymorphism codes for a middle or low MW isoform, then the apo(a) concentration can be high or low, depending upon the *cis*-acting elements. Apo(a) was detected in primate brain, suggesting that Lp(a) particles (which can also carry APOE) are involved in cerebral lipoprotein metabolism (Ramharack et al., 1996). Furthermore, a recent study found serum concentrations of Lp(a) significantly higher in patients with VaD as well as patients with CVD compared with those in healthy individuals (Urakami et al., 2000). These abnormally high serum levels of Lp(a) seemed to be associated with specific increase in low molecular weight (MW) apo(a) isoforms in Lp(a) that are genetically determined. Several lines of evidence linking clinical expression of AD with cerebral infarct suggest that Lp(a) could be a possible risk factor in the development of AD (Snowdon et al., 1997).

It has been previously suggested by Mooser et al. (2000) that a high Lp(a) level may act as an additional risk factor for late-onset AD in APOEε4 carriers, while Lp(a) may protect against AD in noncarriers older than 80 years. However, the analysis of apo(a) polymorphism in this study did not show any difference in the mean size of apo(a) protein in AD patients compared with controls. In a subsequent study, a polymorphic variant (T3888P) located in the Kringle-IV region of apo(a) gene in a case–control series was tested. This polymorphism of the apo(a) gene is relatively common, and it may have an effect on Lp(a) levels and thus have biological significance (Ogorelkova et al., 2001). Overall, there were no differences between case and controls. However, in the APOE2 positive subgroup, the mutant allele was overrepresented in the cases, suggesting that this polymorphism and others at the apo(a) locus be further studied in relation to AD (Compton et al., 2002). Nonetheless, while the precise mechanism for this interaction is not clear, it may be mediated through the effects of the APOE genotype on plasma lipids rather than through direct interactions between APOE and Lp(a) (Ritter et al., 1997).

We found that Lp(a) serum levels were significantly associated, according to a nonlinear relationship, with an increased risk for AD, independently of APOE genotypes, and dependent on age (Solfrizzi et al., 2002). Very recently, a cross-sectional study showed an independent association of small apo(a) isoforms with both VaD and AD, suggesting that the

small particle size of apo(a) may significantly increase the risk for these conditions. However, the risk difference between patients with VaD and those with AD may indicate a diversity in the role played by apo(a) in these two clinical entities (Emanuele et al., 2004a). Furthermore, operational null alleles, defined by absence of apo(a) isoforms from immunoblots (apo (a) null phenotype), have been described (Ogorelkova et al., 1999). Subjects with null operational alleles have very low apo (a) immunoreactivity in plasma, but little is known about the consequences of carrying apo(a) null phenotype. In a study on 73 sporadic AD patients compared with 73 age- and gender-matched healthy controls, the AD patients with the null phenotype had a delayed age at onset of the disease of those who expressed at least one apo(a) band (mean age at onset: 76.8 versus 66.9 years), without APOE interaction (Emanuele et al., 2004b). Finally, in a group of Italian patients with frontotemporal dementia (FTD), 55.6% of the subjects had at least one apo(a) low MW isoform, compared to 29.9% of nondemented controls (OR: 2.93, 95% CI: 1.42–6.06, $P = 0.003$), suggesting a possible role n mediating susceptibility to FTD of low MW apo(a) isoforms, linked to higher plasma levels Lp(a) (Emanuele et al., 2003). On the contrary, serum Lp(a) levels were not associated with cognitive decline over 3 years within an Italian elderly population (Sarti et al., 2001).

The pathophysiological mechanisms by which elevated Lp(a) could be associated with AD are, at present, unknown. Lp(a) is a LDL-like particle, and a recent study found that increased levels of serum LDL-C in AD patients correlate with brain Aβ N-42 levels, suggesting that LDL-C may influence the expression of AD-related pathology (Kuo et al., 1998). Furthermore, clinical and epidemiological data have shown that chronic inflammation appears as a precursor of symptomatic AD (McGeer and McGeer, 1995), suggesting another possible link between elevated serum Lp(a) and AD. In fact, Lp(a) concentration has been found to be increased by a number of clinical and subclinical chronic inflammatory disorders (Baggio et al., 1998). Finally, recent studies have shown that clinical expression of AD is facilitated by cerebral ischemia. In subjects with neuropathological brain lesions typical for AD, brain infarcts, and especially lacunar infarcts, more often resulted in clinical dementia (Snowdon et al., 1997). It was reported that amyloid precursor protein activity and βA production increase in the hippocampus of rodents after severe, transient ischemia (Hall et al., 1995). Since increased Lp(a) serum levels generally enhanced the risk of stroke (Zenker et al., 1986), this may play a role in determining clinical AD.

In conclusion, at present, there are some evidence that higher Lp(a) levels could be linked with AD (Mooser et al., 2000; Solfrizzi et al., 2002), although these abnormally high serum levels of Lp(a) in dementia seemed to be associated with specific increase in low MW apo(a) isoforms that are genetically determined. In fact, there are studies suggesting an increased presence of low MW apo(a) isoforms in AD, VaD, and FTD (Emanuele et al., 2003, 2004a,b; Mooser et al., 2000; Urakami et al., 2000). Larger clinical studies involving patients with predementia syndrome and non-AD dementias, as well as longitudinal studies of AD patients, are needed to confirm the relationship between Lp(a) concentrations and dementia.

7. Serum apolipoprotein E and risk of dementia

Several mechanisms have been proposed to explain the effect of APOE in the brain of AD subject. These include isoform specific toxicity, APOE4-mediated amyloid aggregation, APOE4-mediated tau hyperphosphorylation, and isoform driven APOE concentration changes. The ladder hypothesis is based on an old cardiovascular literature showing that the APOE concentration in serum varies according to individuals apoE genotype (Utermann et al., 1980). As shown previously in healthy individuals (Utermann et al., 1980), APOE concentrations in the plasma or brain of AD subjects are driven by the subject's APOE genotype according to a standard gradient: E2 > E3 > E4. This is consistent with the notion that, in addition to structural changes in APOE isoforms, quantitative alterations of protein levels are crucial to the proper maintenance of brain lipid homeostasis.

The APOE ε4 allele is associated with high TC, LDL-C, and apolipoprotein B levels in many populations (Boerwinkle and Utermann, 1988), and with increased risk of AD, earlier age of AD onset, increased amyloid plaque load, and elevated levels of Aβ40 in the AD brain (Gomez-Isla et al., 1996; Mann et al., 1997). Furthermore, physiological serum APOE concentrations vary between 30 and 250 mg/L (Siest et al., 1995), and have been shown to modulate lipid metabolism (Bohnet et al., 1996). An increase in serum APOE levels in early-onset AD and LOAD patients in comparison with controls was also observed (Taddei et al., 1997). Increased serum APOE levels in AD could be of interest, as APOE concentration is related to vascular disease (Couderc et al., 1993), and there is growing evidence that vascular factors play a role in the etiology of AD.

To date, the results on serum APOE levels in AD are controversial. In a recent study, we found that, in young health subjects, age-matched controls, centenarians, and AD patients, the presence of the APOEε4 allele is associated with lower, and the ε2 allele with higher serum APOE levels (Panza et al., 2003). In the normal population, serum APOE levels are higher when the APOEε2 allele is present, furthermore APOE ε2/2 genotype showed the highest APOE levels (Boerwinkle and Utermann, 1988), and the APOEε4 allele being associated with less APOE protein in plasma (Schiele et al., 2000). An increase in APOE concentrations has been reported in AD patients (Taddei et al., 1997). Furthermore, in a recent study on late-onset AD patients from Northern Italy, serum APOE levels were similar in patients and controls (Scacchi et al., 1999), and a postmortem study confirmed these results (Kuo et al., 1998). Our data are in contrast to these findings, and consistent with other, in which serum APOE level differences between AD patients and controls mainly result from the distribution of the APOE genotypes (Slooter et al., 1998). We found lower serum APOE levels, and higher ε4 allele frequency in our AD patients compared to age-matched controls, but these differences were statistically significant only for APOE genotypes. In fact, in a larger sample as that of the Rotterdam study (Slooter et al., 1998), serum APOE levels were significantly lower in AD patients adjusting for age and gender and were on the borderline of statistical significance adjusting for BMI, protein, and albumin levels. In another recent study,

APOE concentrations were lower in AD patients and non-demented controls with ε4 allele than in those without the ε4 allele (Lehtimaki et al., 1995). Finally, a study conducted on nine European populations showed a clear decrease in APOE serum levels in AD cases, but ε4 and APOE concentration seems to be independently associated with the development of AD, though without adjustment for other lipid parameters (Siest et al., 2000). These contrasting findings in the regulatory role of APOE polymorphism on APOE serum levels in AD were explained by the authors with geographical and age differences in different studies. We suggest the first as source of variability (Panza et al., 1999), because of our data in centenarians demonstrate that the impact of APOE genotype on APOE serum levels is present across all age categories. Finally, the ratio of APOE4 protein to APOE3 protein in the plasma of heterozygous APOE ε3/ε4 individuals did not correlate with AD diagnosis (Fukumoto et al., 2003).

Recent analyses of the promoter area of the APOE gene revealed the presence of distinct polymorphisms that affect the production and secretion of APOE in vitro (Lambert et al., 2000). It is thus conceivable that the APOE ε4 allele-APOE levels association is the result of a linkage disequilibrium between the E4 allele and the promoter variant that controls cellular APOE production. Published reports on CSF APOE levels in AD suggest either increased, decreased, or unchanged levels of APOE when compared to age-matched control subjects (Poirier, 2005). Technical difficulties and excessive standard errors have been invoked to explain the discrepancies between tissue and CSF genotype effect. The reduction in APOE concentrations in brain tissues of APOE4 carriers has been more consistent and is in agreement with the reported genotype-dependent concentration profiles observed in serum of healthy and AD individuals. In a more extreme form of APOE deficiency, the APOE knockout mice give us important insights as to the potential role of APOE in the maintenance of synaptic integrity and plasticity in the CNS. The complete absence of APOE in the brain was shown to compromise both synaptic density and reinnervation in the adult mice whereas reintroduction of the human APOE3 gene driven by the mouse promoter (APOE3 knockin mice) completely prevented synaptic loss in the hippocampus. Furthermore, successful synaptic remodeling in wild type mice and rats is associated with overexpression of APOE in the specific brain areas undergoing active reinnervation and synaptic remodeling (Poirier, 2005). Interestingly, the aging apoE knockout mice exhibit several pathopysiological characteristics of the human apoE4 AD subjects: loss of cholinergic function, excessive lipid peroxydation, cognitive dysfunction, age-dependent synaptic loss, and abnormal tau phosphorylation. Amyloid deposition in the brain is not a feature of this animal model of cognitive deficit.

Our results (Panza et al., 2003) in conjunction with other evidence (Lehtimaki et al., 1995, Slooter et al., 1998; Scacchi et al., 1999) suggested that, at present, serum APOE levels could not be used as a biochemical marker for AD instead of APOE genotyping in neuroepidemiological studies. In fact, there was no consistent association of serum or plasma apoE protein levels with diagnosis when controlled for APOE genotype. Further studies are needed to investigate in depth the role of different common APOE polymorphisms in controlling serum APOE levels in AD.

8. Conclusions

The "vascular hypothesis" is a rapidly growing theory for the pathogenesis of LOAD, suggesting vascular risk factors as a key part of AD pathology. In fact, recent studies suggest that microvascular disorder may contribute to AD pathogenesis and synergistically to cognitive decline related to AD pathology, but the role of cerebrovascular pathology in AD is a matter of controversy. Furthermore, many of the risk factors for CVD and VaD, including circulating factors such as serum/plasma TC, LDL-C, Lp(a), and serum APOE levels, or vascular-related diseases such as diabetes mellitus, atrial fibrillation, hypertension, and atherosclerosis, have also been shown to increase the risk of AD.

The relationship between cholesterol and AD is quite confusing, and at times contradictory. In fact, as seen above, some studies reported that high TC is a risk factor for dementia in midlife, but not in late-life, and high TC in late-life may be an indicator of better health status (Beckett et al., 2000; Simons et al., 2001). One potential explanation for these heterogeneous results is whether TC was assessed in midlife or late life, and the time elapsed between TC measurements and the onset of dementia. In fact, several studies have suggested that high TC in midlife (Martin et al., 1986; Klag et al., 1993), but not late life (Kronmal et al., 1993; Krumholz et al., 1994), is associated with an increased risk of cardiovascular disease, suggesting a similar timing phenomenon for cholesterol and the risk of dementia. Moreover, it can suppose that those who survive to old age with high cholesterol may be a more robust and select population and therefore relatively invulnerable to the potential adverse effects of high TC, including dementia. Nonetheless, studies of cholesterol in old age have had short follow-ups, and this can lead to unclear conclusions regarding the direction of the cholesterol–dementia association.

Given the genetic complexity of AD, the presence of additional genes with influence on the levels of AD-related lipid risk factors is very likely. In fact, at present, several studies have demonstrated the dependence of APOE serum levels upon the APOE genotype, suggesting that serum APOE levels could not be a credible risk factor or a biochemical marker for AD instead of APOE genotyping. In addition, there are some evidence that higher Lp(a) levels could be linked with AD, although there are studies suggesting an increased presence of low MW apo(a) in various forms of dementia, that genetically determined elevated Lp(a) levels. Thus, future research should include genetic information in the establishment of AD-related risk factors or biomarkers (Papassotiropoulos and Hock, 2002).

Several lipid plasma or serum measures are responsive to medications, for instance statins reduce cholesterol and 24S-hydroxy-cholesterol levels. Several observational studies have suggested that statins lower the probability of dementia (thus far unsupported by clinical trials) and that lowering cholesterol may reduce Aβ in the brain (Wolozin, 2004), but the results of these studies are inconclusive. The prevailing wisdom is that high TC is a risk factor for dementia. However,

the relationship between cholesterol and dementia may vary considerably depending on when cholesterol is measured over the life course. It is important to determine the basis for this association, especially given the increasing interest in controlling cholesterol among the elderly. If high TC plays a protective role against dementia in the elderly, then the risk-benefit ratio of lipid-lowering drugs in this population may need to be reevaluated. Likewise, for agents such as nonsteroidal anti-inflammatory agents or antioxidants to exert their putative protective effects against dementia, it might be necessary for them to be taken during or before midlife. Given that the timing of the exposure may be critical, more studies with long-term follow-up and serial assessments of TC are needed to further clarify the causal relationship between cholesterol and dementia.

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