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Carotid artery intima media thickness: a predictor of cognitive impairment?

Christian Saleh

25 bis rue des Envierges, 75020 Paris, France

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1. ABSTRACT

The conversion rate of cognitive impairment to Alzheimer's disease is 1 to 25% per year. Early detection of cognitive impairment will thus become a major concern, particularly when pharmacological intervention for preventing or delaying conversion will prove effective. If simple carotid artery intima media thickness (IMT) measurements were to predict cognitive impairment, IMT could become one of the detection tools, as it is inexpensive, reliable and non-invasive. Since no review paper on this subject is available, a systematic review of the literature was performed. Twenty studies were identified evaluating the association between IMT and cognitive impairment and fourteen found a significant association after multivariate analysis. However, currently no definitive evidence of an association between increased IMT and cognitive impairment can be established. A consensus regarding the precise definition of cognitive impairment, and standardized methods to assess early cognitive impairment alongside a consensus for IMT measurement are needed in future epidemiological studies on the relationship between IMT and cognitive impairment.

2. INTRODUCTION

Intima media thickness (IMT) of the common carotid artery (CCA) is increasingly considered as a marker for early atherosclerosis (10, 11, 42, 47) and vascular diseases, such as stroke, myocardial infarction and peripheral arterial disease (10, 47, 48). Atherosclerosis has been associated with dementia (29) and increased IMT values of the CCA have been correlated with parenchymal changes of the brain observed in dementia, such as leukoaraiosis (12,13, 66), making IMT a potential risk marker of cognitive impairment. However, the specific relationship between IMT and cognitive impairment remains poorly understood. Since no review paper on this subject is available, a systematic review of the literature was performed.

3. METHODS

A PubMed search from 1980 to 2009 was conducted. Key words were "intima-media thickness", "IMT", "wall thickness", "carotid atherosclerosis", "carotid stenosis" used in combined search with

"neuropsychological test", "dementia", "cognitive impairment", "cognition", "cognitive decline" and "Alzheimer". The author aimed to select studies that evaluated the correlation between IMT and cognitive impairment. The electronic search resulted in 155 studies, of which 17 studies fulfilled the selection criteria. Three additional studies were identified through a manual search of retrieved references. All studies were subsequently classified and tabulated according to study design, patient demographics, IMT measurement methods, cognitive impairment criteria, as well as applied methods for cognitive assessment. In this review, 12 studies were cross-sectional (4-7, 60, 61, 63, 67-70, 72), four longitudinal (2, 3, 8, 9) population-based investigations, and four were both cross-sectional and longitudinal (1, 62, 65, 71).

4. RESULTS

4.1. Inclusion and exclusion criteria

Inclusion and exclusion criteria among studies varied to a high extent (Table 1). As increased IMT values were associated with stroke (47, 51), and stroke was correlated with cognitive impairment (29, 53-59), stroke might be a confounding factor. Therefore, studies reporting on IMT were distinguished primarily between post-stroke investigations and stroke-free investigations. Two studies (2, 9) considered stroke or transient ischemic attack (TIA) as their inclusion criteria. Twelve studies specified stroke as an exclusion criteria (1, 3-5, 61, 62, 65, 67-70,72). Other exclusion criteria were Parkinson's disease (2), Alzheimer's disease (2, 60), neoplasia (7, 60, 62), aphasia (2, 9), hypertension (60), dementia (62, 67), fasting total plasma homocysteine (Hcy) < 8.5 μmol/L (69) and ischemic heart disease (60). Three studies (6, 8, 71) did not report on this aspect.

4.2. Cognitive decline and cognitive impairment definitions

Definitions and assessment tools of cognitive decline and impairment varied across studies (Table 2). For screening purposes most frequently the Mini-Mental-Status Examination (MMSE) was used (1, 2, 4-6, 8, 9, 60, 62, 63, 65, 68, 70, 72). In addition to MMSE a variety of cognitive function assessment tools were applied, among which were the Digit Symbol Substitution Test (1, 4), the Montgomery-Asberg Depression Rating Scale (2) and the Dementia Rating Scale (5, 68). The majority of studies used an MMSE cut off score of twenty-four or less as indicative of cognitive impairment (2, 4, 9, 60, 62). A different cut-off score, less than twenty-six, was used in three studies (6, 8, 63). In one study, using the modified MMSE (1), cognitive impairment was defined by a score of less than 80/100, and cognitive decline "as an average decrease in Modified Mini-Mental State Examination score of more than 1 point per year". The cut-off scores for cognitive decline and cognitive impairment were not mentioned in nine studies (3, 5, 7, 61, 67-70, 72).

4.3. Neuroimaging

MRI or CT brain scanning were reported in six studies (1, 2, 6, 8, 9, 60, 65, 67, 68), assessing mainly for signs of ischemic stroke. Ten studies (3-5, 7, 61-63, 70-72) did not report on brain imaging.

4.4. Methodology for intima media measurement

There were a variety of methodological heterogeneity across the studies regarding IMT measurement for selected carotid artery segments (CCA, CA bulb, ICA) and carotid artery wall (near versus far) (Table 3). For IMT measurement, the CCA was used in the majority of studies (1, 2, 4-8, 60, 63, 65, 68-72). The IMT of the CA bulb was measured in one study (62), and three different locations (CCA, CA bulb, ICA) were evaluated in four other studies (3, 9, 61, 67). IMT was measured most frequently at the far wall of the CCA (2, 4, 5, 60, 63, 68, 69, 71). The far wall IMT of the CA bulb was measured in one study (62). IMT was evaluated at the far and near walls of the CCA in four studies (1, 8, 65, 72). The IMT of the near and far walls of three carotid artery segments (CCA, CA bulb, ICA) were measured in four studies (3, 9, 61, 72).

4.5. IMT and cognitive impairment

Although the methodology and study design of the 20 reported studies differed significantly, certain patterns could be noted. These patterns became more evident by differentiating the studies in post-stroke cohorts and cohorts free of vascular events.

4.5.1. Series of patients with stroke

4.5.1.1. Positive association between intima media thickness and cognitive impairment

In a longitudinal study with a one year follow-up period, Talelli *et al.* (2) found that IMT was significantly associated with cognitive impairment at one-year defined by a MMSE score < 24 and after multivariate analysis. One further study (9) found that IMT was univariately associated with a six-month change in the MMSE in the control-group (45 participants), but not in the case-group (110 participants).

4.5.2. Series of patients without stroke

4.5.2.1. Positive association between intima media thickness and cognitive impairment

After a five years follow-up Johnston *et al.* (1) reported that increased IMT on left and right CCA were associated with increased risk of cognitive decline in univariate analysis. After adjusting for controlateral stenosis, demographics and traditional vascular risk factors, the associations were attenuated and remained significant only for the left CCA (borderline association). The Atherosclerosis Risk in Communities (ARIC) study (61) found a cross-sectional association between carotid IMT with 2 out of 3 cognitive function scales. Carotid IMT (C-IMT) was inversely associated with the Delayed World Recall Score in men and inversely correlated with the Digit Symbol Score in both genders. In a further cross-sectional study, Romero *et al.* (67) showed that higher internal carotid artery IMT was associated with poorer performance on the executive function factor and the nonverbal memory factor. The authors reported that the association became significant for the verbal memory factor, remained significant for the nonverbal memory factor, and was borderline for the executive function factor, after full

Table 1. Demographics

Sample size	Gender	Average Age (SD)	Inclusion Criteria	Exclusion Criteria	Reference
4006	Female: 2427 Male: 1579	74.7	Right-handed subjects	1. History of CVA 2. History of TIA 3. Carotid endarterectomy	1
171	Female: 70 Male: 101	66 (11.5)	Stroke	1. Other language than Greek 2. Diseases affecting cognition 3. Severe medical illness 4. Clinical evidence of concomitant Alzheimer's disease 5. MMSE < 24 6. Residual aphasia at 1 year post-stroke	2
10963 (ARIC longitudinal study)	Female: 6.126 Male: 4.837	58.5	Cardiovascular risk factors	1. History of CVA 2. History of TIA	3
1279	Female: 753 Male: 526	65.0 (3.0)	NM	CVA	4
109	Female : 46 Male : 63	69.18	1. CAD 2. AP 3. Previous MI 4. HF 5. Cardiac surgery 6. Arrhythmia 7. Hypertension	1. Neurological disorder 2. Psychiatric disorder 3. Substance abuse 4. Dementia Rating Scale <123	5
1. Dementia group: 248 2. Not demented group: 1698	1. Demented group: Female: 202 Male: 82 2. Not demented group: Female: 1075 Male: 623	1. Demented group: 82.65 2. Not demented group: 70.9	1. Dementia 2. Non dementia	NM	6
Case: 47 Control: 40	Case: Female : 6 Male:41 Controls: Female:21 Male: 19	Case: 46 (12) Controls: 42 (12)	Age > 18	1. Opportunistic systemic or CNS infection 2. CNS neoplasm 3. Active alcohol/drug abuse 4. Aphasia 5. Concomitant neurological disease 6. Psychiatric diseases	7
6.647	Female: 3921 Male : 2726	72.4	Age > 55	NM	8
Case: 110 Control: 45	Case: Female: 35 Male: 75 Control: Female: 23 Male: 22	Case: 55.6 Control: 53.3	Case: 1. First ischemic CVA or TIA 2. Age>45 y 3. Absent neurological / psychiatric disorder Control: 1. No clinical signs of CVA 2. One or more vascular risk factors	1. Aphasia 2. MMSE $\leq$ 20 3. Subjective or objective memory complaints	9
Case: 35 Control: 25	Female: 18 Male: 42	78.5	Case: Vascular Dementia Control: No dementia	1. Alzheimer's disease 2. Diabetes Mellitus 3. Hypertension 4. Severe medical condition 5. Cancer	60
13913 (ARIC cross sectional study)	Female: 7652 Male: 6261	57	Cardiovascular risk factors	1. Antipsychotic medication 2. History of Stroke 3. History of TIA 4. Outside study age	61

91	Female: 91	65	NM	1. Stroke 2. Cancer 3. Musculoskeletal disease 4. Dementia	62
400	Male: 400	60	Independent living	Mental/Physical inability to attend study centre	63
66	Female: 36 Male: 30	72.7 (6.1)	1. AD 2. Mild to moderate CI	1. CVD 2. Stepwise progression of CI 3. Focal neurologic signs 4. MRI: 4.1. Cortical infarction 4.2. LWML	65
1971	Female: 1044 Male: 927	58 (10)	NM	1. CVA 2. Dementia 3. Multiple Sclerosis 4. Neurological conditions affecting MRI	67
88	Female: 41 Male: 47	70 (7.7)	Cardiovascular disease	1. Neurologic disease 2. Substance abuse 3. Major psychiatric disease	68
504	Female: 196 Male: 308	60.8 (9.9)	1. > 40 years 2. Plasma Hcy ≥ 8.5 µmol/L	1. CVD 2. DM 3. Hypertension 4. Untreated thyroid disease	69
3896	Female: 1088 Male: 2808	60.9	NM	NM	70
3386	Female: 2000 Male: 1386	67.7	NM	NM	71
Case: 63 Control: 64	Case: Female: 37 Male: 26 Control: Female: 42 Male: 23	Case: 75.7 (9.2) Control: 75.7 (8.6)	Case: 1. AD 2. aMCI Control: 1. No evidence of neurological disease	Case / Control: 1. Major vascular disease 2. Chronic alcohol intake / smoking 3. Drugs increasing Hcy	72

CVA = Cerebral Vascular Accident, CVD = Cerebrovascular disease, MRI = Magnetic Resonance Imaging, Hcy = Homocysteine, DM = Diabetes Mellitus, LWML = Large White Matter Lesions, TIA = Transient Ischemic Attack, aMCI = amnestic Mild Cognitive Impairment, CAD = Coronary Artery Disease, AD = Alzheimer Disease, CI = Cognitive Impairment, MI = Myocardial Infarction, HF = Heart failure, NM = Not Mentioned, f = female, m = male, ARIC = Atherosclerosis Risk in Communities study

multivariable adjustment. However, the authors noted that common carotid artery IMT was not associated with any of the cognitive measures. Cohen *et al.* (68) described in their cross-sectional study that increased IMT was strongly related to reduced attention, executive function, and information-processing speed. In a further cross-sectional study, Muller *et al.* (63) found an increased IMT to be associated with lower memory performance using the Rey auditory verbal learning test and the Doors test to assess for verbal episodic and visual memory. Haley *et al.* (5) underlined that a C-IMT cut-off of ≥ 0.9 mm might be relevant before higher IMT consistently relates to risk of cognitive impairment. The authors found in their cross-sectional study that an increased IMT was associated with lower attention-executive-psychomotor functioning in non-demented patients, while it was not significantly related to language, memory, or visual-spatial abilities. Komulainen *et al.* (62) described in their small prospective study of 91 elderly women that carotid IMT was associated with poor memory in cross-sectional and longitudinal analysis, and with cognitive speed only in the longitudinal analysis, but not with global cognitive function (assessed by the MMSE).

4.5.2.2. Negative association between IMT and cognitive impairment

In a cross-sectional study, Johnston *et al.* (1) reported that high IMT on the left or right CCA were associated with an increased risk of cognitive impairment in univariate analysis. However after adjustment for contralateral stenosis, demographics, and traditional vascular risk factors, these associations were modified and were no longer statistically significant. The ARIC study (3) found that IMT was longitudinally not associated with cognitive function test impairment in subjects aged 45-69 years. No association between IMT and cognitive decline after adjusting for confounding factors could be found in the cross-sectional study of Auperin *et al.* (4).

5. DISCUSSION

The burden of cognitive impairment and Alzheimer's disease in industrialized countries will become a major public health and economic issue. The reported rate of conversion of cognitive impairment to Alzheimer's disease is 1 to 25% per year (18). Thus, early detection of

Table 2. Cognitive Status Assessment

Cognitive Impairment	Cognitive Function Assessment	Reference
MMSE < 80/100 DSST: Impairment < 19	1. Modified MMSE 2. Digit Symbol Substitution Test (DSST)	1
MMSE < 24	1. MMSE 2. MADRS	2
NM (ARIC longitudinal study)	1. Delayed word recall 2. Digit symbol subtest of the Wechsler Adult Intelligence Scale-Revised 3. First-letter word fluency	3
MMSE < 24	1. TMT, part B 2. DSST from WIS-R 3. PASAT: Auditory attention 4. BVRT: Visuospatial perception 5. Verbal Fluency 6. RPM	4
NM	1. MMSE 2. Language: Boston naming Test, Category Fluency for Animals 3. Visual-spatial 4. Memory: California verbal Learning Test, Complex Figure Test, Brief Visual Memory Test-Revised 5. Attention-executive psychomotor: Trail Making Test, p A and p B, Stroop-Word, WAIS-III Digit Span and Coding	5
1. MMSE ≤ 25 2. GMS-A ≥ 1 3. CAMDEX < 80	1. MMSE 2. GMS-A 3. CAMDEX 4. DMS-III-R	6
NM	1. Trail Making Test A and B 2. Digit Span Memory Test 3. Corsi Block Tapping Test Visual working memory and visual short term memory 4. Memory Test A and B	7
MMSE < 26	1. MMSE 2. Geriatric Mental State schedule (GMSS)	8
MMSE < 24	1.Montreal Cognitive Assessment 2. MMSE	9
MMSE< 24	MMSE	60
NM (ARIC cross-sectional study)	1. Delayed Word Recall Test 2. Digit Symbol Subtest of WAIS-R 3. Word Fluency of Multilingual Aphasia Examination	61
MMSE< 24	1. MMSE 2. Word Recall Test 3. Stroop Test 4. Letter-Digit Substitution Test	62
MMSE< 24-26	1. MMSE 2. Rey auditory verbal learning test 3. Doors test 4. Digit Span Test (subtest of WAIS) 5. Dutch Adult Reading test	63
DRS <2	1. DRS 2. MMSE	65
NM	1. Wechsler Memory Scale Logical Memory 2. Halstead Reitan Trail Making Tests A and B 3. Boston Naming Test	67
NM	1. MMSE 2. DRS 3. Boston Naming Test 4. Block Design total 5. California Verbal Learning Test	68
NM	1. Symbol Digit Modalities Test 2. Trail Making Test Part B 3. Wechsler Memory Scale, 3rd Edition 4. Category fluency 5. Boston Naming Test	69
NM	1. Alice Heim 4-I 2. Mill Hill Vocabulary test 3. MMSE	70
6CIT > 7	1. 6CIT 2. GDS	71
NM	1. MMSE (Italian Version) 2. Mental Deterioration Battery	72

MMSE = Mini Mental Status Examination, GMS-A = Geriatric mental state examination, DSST = Digit Symbol Substitution Task, RPM = Raven Progressive Matirices, TMT = Trail-Making Test, NM = Not Mentioned, DSM-III-R = Diagnostic and statistical manual of mental disorders, Third Edition-R, GMS = Geriatric Mental State examination, CAMDEX = Cambridge Mental Disorders of the Elderly Examination, DRS = Dementia Rating Score, 6CIT = 6 Item Cognitive Impairment Test, GDS = Geriatric Depression Scale, ARIC = Atherosclerosis Risk in Communities study

Table 3. Intima media thickness (IMT)

Echography equipment	Site of IMT measurement	Selected CA wall for IMT measurement	Side of IMT measurement	Reference
High resolution B-mode system	CCA	Near / Far	Bilateral	1
ATL, HDI 3500 with 12-5 linear transducer	CCA	Far	Bilateral	2
High resolution B-mode system (ARIC longitudinal study)	1. CCA 2. CB 3. ICA	Near / Far	Bilateral	3
High-resolution B-mode system, Aloka SSD-650 with 7.5-MHz transducer	CCA	Far	Bilateral	4
High resolution B-mode system, Agilent 5500 with 7.5-MHz transducer	CCA	Far	Left	5
Ultrasound with 7.5 MHz linear-array transducer	CCA	NM	Bilateral	6
Ultrasound (Siemens Sonoline Elegra)	CCA	NM	Bilateral	7
B-mode system	CCA	Near / Far	Bilateral	8
Doppler ultrasound with linear 8 MHz transducer.	1. CCA 2. CB 3. ICA	Near / Far	Bilateral	9
High Resolution B-mode system with 7.5-MHz linear-array transducer	CCA	Far	Bilateral	60
High Resolution B-mode system (ARIC cross-sectional study)	1. CCA 2. CB 3. ICA	Near / Far	Bilateral	61
High-resolution system with 10-MHz transducer	CB	Far	Bilateral	62
Ultrasound with 7.5 MHz transducer	CCA	Far	Bilateral	63
NM	CCA	Near / Far	Bilateral	65
System with high-resolution linear-array transducer with color Doppler and Doppler spectral analyzer / CCA: 7.5-MHz transducer CB, ICA: 5-MHz transducer	1. CCA 2. CB 3. ICA	Near / Far	Bilateral	67
High-resolution B-mode system, Agilent 5500, with 7.5-MHz transducer	CCA	Far	Left	68
High-resolution B-mode system	CCA	Far	Right	69
High-resolution system, Aloka 5500 with 7.5 MHz transducer	CCA	NM	Bilateral	70
NM	CCA	Far	NM	71
IU 22 Philips system	CCA	Near / Far	Bilateral	72

CA = Carotid Artery, CCA = Common Carotid Artery, ICA = Internal Carotid Artery, CB = Carotid Bulb, IMT = Intima-Media Thickness, NM = Not Mentioned, '/' = and, ARIC = Atherosclerosis Risk in Communities study

cognitive impairment will become a major concern, particularly when pharmacological intervention for preventing or delaying conversion will prove effective (14, 23). Cerebral vessel atherosclerosis is assumed to be associated with cognitive impairment through the consequences of chronic brain hypoperfusion (73, 74). Therefore, if simple IMT measurements were to predict cognitive impairment, IMT could become one of its detection tools, particularly because it is inexpensive, reliable and non-invasive. This systematic review identified twenty studies that evaluated the association between IMT and cognitive impairment and fourteen (1, 2, 5, 6, 9, 62, 63, 65, 67, 68-72) were significant after multivariate analysis. This lack of a strong relationship may in part be related to the variability in defining cognitive impairment and the heterogeneity in IMT measurement methodologies. The prime difficulty consists in defining mild cognitive impairment (MCI), differentiating normal aging from mild cognitive impairment, and differentiating mild cognitive impairment from mild dementia (15, 18, 20, 21, 44, 46). MCI, a term that appeared for the first time in the literature in 1990 (43), is not considered an established diagnosis with a single set of criteria, but rather a heterogeneous condition, for which several criteria, in recent years, were suggested (16, 17, 19, 21, 22, 44, 45). Currently MCI is a diagnosis of exclusion for patients not fulfilling the criteria of Alzheimer's disease (AD) or dementia, but who exhibit some form of cognitive impairment (specifically with memory loss, "amnestic" MCI) (18, 21, 44).

There is also a lack of consensus regarding definition and standardized measures to assess MCI (25, 26, 28, 44, 45) as well as scarce knowledge of the degree of agreement between the commonly used tests in assessing for cognition (MMSE, DSM-4, ICD-10, MDRS) (24, 27, 29). The most frequently used test in this review was the Mini Mental Status Examination (MMSE). The MMSE is considered a valuable screening instrument for the initial, formal assessment of cognition (30, 31). However, it is a tool that lacks the necessary detail for the differentiation between mild cognitive impairment and early onset dementia, especially in well educated subjects (30, 31). Furthermore, patients with visual, hearing and communication impairment(s) can not be evaluated objectively, as the MMSE is largely based on reading, writing and verbal response skills (75-77).

Consequently, in the twenty studies included in this review, a comparison of the reported results is made difficult because of the use of different cognitive tests, each

evaluating a different cognitive domain. This in part could explain the divergent association with IMT. MCI is assumed to be of degenerative origin (33-36). Ten of the twenty studies (1, 3, 4, 7, 8-9, 61-63, 71) included in this review did not report on the aetiology of the observed cognitive impairment. For example, stroke or other aetiologies could have been a confounding factor in the association between cognitive impairment and IMT. Although hippocampal atrophy appears to be associated with MCI (32, 34-36), the routine role of neuroimaging in diagnosing MCI is not established as of yet (37, 49). Structural volumetric magnetic resonance imaging (MRI), single photon emission tomography (SPECT), positron emission tomography (PET) are at present the neuroimaging modalities most commonly used in patients with MCI (37, 49). The majority of the papers in this review (1, 3, 4, 7-9, 61-63, 71, 72) did not report on focused neuroimaging studies to detect specific brain alterations to sustain their diagnosis of mild cognitive impairment.

There was a huge variability in methods of IMT measurement, with regard to location, referenced IMT values and measurement techniques. This heterogeneity made it difficult to directly compare IMT results in these twenty studies. Another important methodological issue in the reviewed studies was the lack of control groups (1-5, 8, 61-63, 65, 67-71). The question of test-retest effect remains unanswered. A further limiting factor were the modest sample sizes in several studies (2, 5-7, 9, 61-63, 65, 68, 72) which consequently reduced study power and limited the generalizability of the findings. Currently, no definitive evidence of an association between increased IMT and cognitive impairment can therefore be made. Differences in age, inclusion criteria, study design, and length of follow-up may have accounted for the conflicting results. However, the present results from the investigation into the relationship between IMT and cognitive impairment remain promising. Fourteen out of the twenty reviewed studies showed a significant association after multivariate analysis (1, 2, 5, 6, 9, 62, 63, 65, 67, 68-72). Future research must establish whether increases in IMT, especially at early stages, does in fact exclusively represent atherosclerosis (10, 12, 38-40, 50, 52, 64, 78). There is also an imperative need for a consensus regarding the precise definition of cognitive impairment and the use of standardized methods in the assessment of early cognitive impairment (25), alongside a uniform way to perform IMT measurements (78) for future epidemiological studies on the relationship between IMT and cognitive impairment.

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Send correspondence to: Christian Saleh, 25 bis rue des Envierges, 75020 Paris, France, Tel: 0033679777656, E-mail: chs12us75010@yahoo.com

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