European Review for Medical and Pharmacological Sciences 2014; 18: 1778-1789

Diabetes mellitus and dementia – a systematic review and meta-analysis

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Abstract. – OBJECTIVES: Diabetes mellitus and dementia, two of the most common disorders in the elderly, are posing a tremendous burden on public health in the society. Moreover, the absolute number and the proportion of older people who are affected by diabetes, borderline diabetes and dementia are expected to further increase over the next few decades. The aim of this study was to determine if a relationship existed between type 2 diabetes and dementia by performing a meta-analysis of published cross-sectional and prospective studies.

MATERIALS AND METHODS: Comprehensive literature search was performed and the extracted data was analyzed.

RESULTS: Our findings highlight the need to detect borderline diabetes and undiagnosed diabetes in order to effectively prevent dementia, as previous studies have shown that prediabetes and diabetes could be improved by interventions addressed towards lifestyle changes and antidiabetic treatment.

CONCLUSIONS: As far as clinical practice is concerned, it is important to bear in mind that prevention, timely diagnosis, and the optimum treatment of diabetes and borderline diabetes may help to reduce the occurrence of dementia.

Key Words:

Type 2 diabetes, Dementia, Systematic review, Meta-analysis, Diabetes and dementia, Prevent dementia, Optimum treatment of diabetes, Borderline diabetes.

Introduction

The aging of populations has become a worldwide phenomenon1. In 1990, 26 nations had more than two million elderly citizens aged 65 years and older, and the projections indicate that an additional 34 countries will join the list by 2030. In 2000, the number of old people (65+ years) in the world was estimated to be 420 million and it is projected to be nearly one billion by 2030, with the proportion of old people increasing from 7 to 12%. The largest increase in absolute numbers of old people will occur in developing countries; it will almost triple from 249 million in 2000 to an estimated 690 million in 2030. The developing regions' share of the worldwide aging population will increase from 59 to 71%[2]. Developed countries, which have already shown a marked increase in people over 65 years of age, will experience a progressive aging of the elderly population. Underlying global population aging is a process known as the "demographic transition" in which mortality and then fertility decline[3]. Decreasing fertility and lengthening life expectancy have together reshaped the age structure of the population in most regions of the planet by shifting relative weight from younger to older groups.

Consequently, both developed and developing countries will face the challenge of coping with a high frequency of chronic conditions, such as dementia, which are characteristic of aging societies. These conditions impair the ability of older persons to function optimally in the community and reduce well-being among affected individuals and their families. Further, these conditions are associated with significant health care costs that must be sustained by the society at large. Thus, the global trend in the phenomenon of population aging has a dramatic impact on public health, healthcare financing and delivery systems throughout the world[4].

A clustering of interrelated metabolic risk factors such as diabetes mellitus, obesity, hypertension and dyslipidemia has received increasing attention in the past few years. Several components of the metabolic syndrome have been individually related to cognitive outcomes. A prospective study found that the metabolic syndrome contributed to cognitive decline[4,5]. But this finding was not confirmed in a population of the oldest old. The concept of the metabolic syndrome may be less valid in this age group[5]. Finally, a cross-

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sectional study showed that metabolic syndrome was associated with an increased risk of Alzheimer's disease (AD)[6].

A potential link between diabetes and cognitive impairment was first reported more than 80 years ago. The association of diabetes with these cognitive changes is now well established[7]. There is substantial evidence suggesting that type 2 diabetes is associated with cognitive impairment involving both memory and executive function[8-10]. Several large longitudinal population-based studies have also shown that the rate of cognitive decline is accelerated in elderly people with type 2 diabetes[11]. With regard to more profound degrees of cognitive impairment, namely dementia, both cross-sectional and prospective studies suggest that diabetes is associated with an increased risk of dementia, but the issue whether this concerns only vascular dementia (VaD) or also AD is debated. Since diabetes is strongly related to vascular disease, the association between diabetes and VaD is expected.

The current study was carried out to determine if a relationship existed between type 2 diabetes and dementia by performing a meta-analysis of published cross-sectional and prospective studies.

Materials and Methods

Data Sources and Searches

Clinical literatures were identified via Ovid MEDLINE, Ovid EMBASE, SCOPUS, and Cochrane Database (source, 1950 to 2011s). Both database-specific controlled vocabulary and general free text terms were used to maximize retrieval. MeSH terms used were "type 2 diabetes", "dementia", "Alzhiemer's disease", "vascular dementia", and "geriatric patients". Searches were limited to literatures available in full text and humans within a valid limit within the database. Hand searching of key article reference lists was used to locate additional relevant articles. Eligibility assessment and data abstraction were both performed independently in an unblended standardized manned by 2 independent reviewers.

Data Extraction and Analysis

Results from all searches were combined and duplicates were removed. Inclusive criteria were studies describing general data (study design), patients (number of included patients, mean age, gender), type of diagnostic criteria and/or intervention strategy used, timing of determination. The outcomes of the collected manuscripts were synthesized and formed the basis for further analysis and description, which was done following recommendations from the Cochrane Collaboration and the Quality of Reporting of Meta-analyses guidelines. Exclusion criteria were (1) initial diagnosis in reported patients was more than 12 months from entry date into the study, and (2) history of tumorigenesis in included patients that can severely confound conclusions. A meta-analysis of the present and published studies was performed using R Gui version 2.2.1 (available at HYPERLINK "http://www.r-project.org" http://www.r-project.org). The quality of the evidence for a specific outcome was based on the study design, risk of bias, consistency of results, directness (generalizability), precision (sufficient data) and potential bias for the reporting of results across all studies that measured that particular outcome.

Results

Cross-Sectional Studies

As early as 1984, a case-control study was performed to determine the role of prior illness, including diabetes, in the development of AD. The results showed a non-significant association of diabetes with AD. This was followed by several studies which have yielded conflicting results about the association of diabetes with VaD and AD. Table I summarizes 20 cross-sectional studies that have investigated this issue[12-31].

The Rotterdam study is the first population-based cross-sectional study to have used ëdementia' as a variable in association with diabetes, and it found an association of diabetes with VaD, and with AD only in subjects treated with insulin[13]. Most studies have instead examined subjects with either AD or VaD and compared them with each other or with control subjects. A major problem with these first reports is that the most commonly used diagnostic criteria for AD emphasized the exclusion of underlying disorders, particularly cerebrovascular disease. It is not surprising therefore that these studies have tended to report an excess of cerebrovascular risk factors, including diabetes, in VaD group compared to non-demented control or AD groups. Another problem is that cases have been drawn from secondary or tertiary dementia referral centers, which may have introduced some selection bias.

Table I. Major epidemiological studies concerning the association between diabetes and dementia: cross-sectional and retrospective studies. The odds ratios (OR) refertodementia, when not other wisespecified.

Author, year	Country and samples	Age (y)	Diabetes: ascertainment of cases	Dementia: N of cases and diagnostic criteria	Results	Covariates
Stella et al, 2007	Brazil, 78 outpatients	60+	Medicalrecords	VaD (78) ICD-10	23.1% diabetes in Neuroimaging	Not reported VaD cases
Valcour et al, 2005	USA, 203 HIV-1 infected patients	20-76	Self-report,	Dementia (39) Fasting blood glucose	OR 5.4 (1.66-17.70) neuropsychological tests and neurological examination	Age, education, and vascular factors
Beeri et al, 2005	USA, 385 specimen from autopsies, 15.8% diabetics, and 66% female	84	Medical records	CERAD neuropathological categories	Diabetics had fewer neuritic plaques ($p = 0.008$) and NFTs ($p = 0.047$)	Age, dementia severity, and APOE ε4
Haan et al, 2003	USA, 1789 Latinos	60+	Self-report, antidiabetic drugs fasting blood glucose	Dementia (69) AD (31), NINCDS-ADRDA VaD (14), California criteria	43% of dementia risk was attributable to diabetes	Not reported
Bowirrat et al, 2002	Israel, 823 Arabs	60+	Medical records	AD (168) DSM-IV VaD (49)	OR 1.1 (0.6-1.7) OR 1.8 (0.9-3.5)	Univariate analysis
Tariot et al, 1999	USA, 467 long-termcare residents	74.8	Medical records	AD (85) NINCDS-ADRDA VaD (84) Clinical diagnosis	Diabetes was 6.1% in AD, and 47.4% in VaD	Age, sex, and race
Boston et al, 1999	UK, 438 community-based sample	75+	Self-report	AD (222) VaD (34) CAMDEX	A greater proportion of diabetes in VaD ($p = 0.002$)	Age and sex
Brayne et al, 1998	UK, anested case-control study, 36 case and 340 controls	75+	Self-report Diabetes 6% in controls, 16% in cases	Dementia (36) ICD-10 AD (18) CAMDEX Autopsy	OR 2.6 (0.9-7.8) OR 1.4 (1.1-17.0)	Age and sex
Kuusisto et al, 1997	Finland, 980 subjects	69-78	Fasting blood glucose	AD (46), NINCDS-ADRDA	OR1.1 (0.9-2.4)	Age, sex, and education
Heitner et al, 1997	USA, a matched case-control study, 49 diabetics and 52 controls	69.4	Medical records	AD, autopsy neuropathologic diagnoses	Diabetes was not associated with AD pathology	Age and sex
Lindsay et al, 1997	Canada, a matched case-control study, 129 VaD cases and 535 controls	Not shown	Medical records	VaD, DSM-III-R clinical grounds	OR 1.7 (0.9-3.1)	Age, sex, and education

Table continued

Table I *(Continued)*. Major epidemiological studies concerning the association between diabetes and dementia: cross-sectional and retrospective studies. The odds ratios (OR) refertodementia, when not other wisespecified.

Author, year	Country and samples	Age (y)	Diabetes: ascertainment of cases	Dementia: N of cases and diagnostic criteria	Results	Covariates
Nielson et al, 1996	USA, an observational survey, 265 dementia cases	74	Medical records	AD (123) NINCDS-ADRDA VaD (51) California criteria Mixed (57)	Diabetes was 0.8% in AD 11.8% in VaD and 8.8% in mixed dementia	Not reported
Ott et al, 1996	The Netherlands, a population-based study, 6330 subjects	55-99	Antidiabetic drugs, random blood glucose OGTT	Dementia (265) DSM-III-R AD (194) NINCDS-ADRDA VaD (44) NINDS-AIREN	OR 1.3 (1.0-1.9) OR 1.3 (0.9-1.9) OR 2.1 (1.1-4.0)	Age, sex, education, vascular disease
Gorelick et al, 1993	USA, a case-control study, 61 multi-infarcts disease	60+	Medical records	Multi-infarct dementia, DSM-III-R	Diabetes was not related to multi-infarct dementia	Not reported
Landin et al, 1993	Sweden, a retrospective study, 38 AD, 14 VaD and 19 other dementia	Not shown	Medical records	AD (38) NINCDS-ADRDA VaD (14), DSM-III-R, Other dementia (19)	AD cases had lower blood glucose compared with other dementia and VaD	Not reported
Kokmen et al, 1991	USA, a case-control study, 415 cases and 415 controls	Not shown	Medical records	AD (415), Consensus criteria, similar to DSM-III-R	OR 1.2 (0.8-1.8)	Not reported
Broe et al, 1990	Australia, a matched case-control study, 170 AD, and 170 controls	52-96	Self-report	AD (170), NINCDS -ADRDA	OR 0.6 (0.2-1.6)	Univariate analysis
Wolf-Klein et al, 1988	USA, 348 subjects, 173 men and 165 women	62-98	Medical records	AD (75), NINCDS-ADRDA	Less diabetes in AD cases	Not reported
Amaducci et al, 1986	Italy, case-control study, 119 cases, 116 hospital and 97 population controls	41-80	Self-or informant-report	AD (119), NINCDS-ADRDA	OR 0.7 ($p = 0.54$) for hospital controls; 1.0 ($p = 1.0$) for hospital controls	Not reported
Heyman et al, 1984	USA, a matched case-control study, 40 AD cases, 80 controls	51-71	Self-or informant-report	Duke University Hospital Uniform criteria for diagnosis of AD	Diabetes was 7.5% in AD, and 8.8% in controls ($p = 0.84$)	Not reported

In addition, cross-sectional investigation of the association of diabetes with prevalent dementia cases will generally underestimate or even detect an inverse association due to the raised mortality in later life related to diabetes, probably higher in combination with dementia.

Prospective Studies

Population-based longitudinal studies that compared the incidence of dementia between patients with and without diabetes provide more reliable risk estimates than studies on patients with prevalent dementia. Over the last decade, many population-based longitudinal studies have revealed a relationship between diabetes and an increased risk of dementia and VaD, although the results concerning the association of diabetes with the Alzheimer type of dementia are inconsistent. In fact, some prospective studies showed the association between diabetes and an increased risk of AD, or observed such an association only in specific subgroups, and others did not. Nineteen population- based longitudinal studies have examined the relation of diabetes and dementia (Table II)[32-50]. The incidence of any dementia was approximately two-to-three-fold higher in people with diabetes than in those without diabetes in seven of the ten studies reporting this aggregate outcome. This high risk included both AD (eight of fifteen studies including two studies that showed the association of diabetes with AD only in APOE μ4 non-carriers) and VaD (five of seven studies). The limitation of clinical diagnostic criteria in the classification of dementia by pathological subtypes should be considered, especially in a complex disorder such as diabetes. Among these studies, detailed data on modulating or mediating effects of glycemic control, microvascular complications, and comorbidities were generally absent.

Post-Stroke Dementia Studies

The risk of dementia increases after stroke[51]. Diabetes is a major risk factor for cerebrovascular disease. It is likely that the association between diabetes and dementia is mediated or modulated by cerebrovascular disease. Little progress has been made in understanding the role of diabetes in the development of dementia in stroke patients. Studies which have examined the role of diabetes in the development of dementia after stroke have produced conflicting results. Among the ten studies, six showed that diabetes was related to post-stroke dementia (Table III)[52-61]. It has been suggested that if diabetes has an effect on dementia after stroke, it may accelerate the dementia onset rather than increase the longer term risk of the disorder[62]. Another consideration is that the raised mortality associated with stroke in the presence of diabetes may mask the association of diabetes with post-stroke dementia[63].

Borderline Diabetes and Cognitive Impairment

The hypothesis that impaired glucose regulation is related to decrements in cognitive performance is verified by several studies that evaluated the neuropsychological performance in pre-diabetic adults. In 1995, the relationship between impaired glucose tolerance and reduced Mini-Mental State Examination (MMSE) score was first reported[64]. To date, there are few studies that have examined the impact of impaired glucose regulation on cognitive functions. Collectively, five studies have demonstrated the presence of mild cognitive deficits in people with pre-diabetes (Table IV)[63-66]. To the best of our knowledge, no studies have so far investigated the effect of early stage diabetes on the risk of dementia and its major subtypes.

Discussion

Before drawing any conclusions from this meta-analysis, some points need to be taken into account. First, the characteristics of the study populations are different from study to study, especially regarding age and gender. Mortality risk is elevated in diabetes and diabetes-associated diseases. In a higher age range, selected survival might result in milder forms of diabetes being examined with respect to potential dementia. Therefore, it should be emphasized that these results from elderly populations cannot be generalized to younger persons.

Second, different methods of assessment have been used in different studies to identify diabetic patients. A number of studies defined diabetes only based on the information from self-reports, medical records, or the use of anti-diabetic medications, and they did not assess blood glucose concentration. As diabetes is often undiagnosed among elderly people, in these studies, a substantial proportion of people with diabetes might have been erroneously assigned to the non-dia-

Table II. Major population-based prospective studies concerning the association of diabetes with dementia. The relative risk (RR), hazard ratios (HR), odds ratios (OR), or standard mortality rate (SMR) refer to dementia, when not otherwise specified.

Author, year	Country and study population	Age (y)	Follow-up (y)	Diabetes: ascertainment of cases	Dementia: N of cases and diagnostic criteria	Results	Covariates
Irie et al, 2008	USA, The Cardiovascular Health Study Cognition Study, 2547 dementia-free subjects	74.4	5.4	Anti diabetic drugs Fasting blood glucose 320 (12.6%) diabetes	Dementia (411) MRI AD (207) NINCDS-ADRDA Mixed AD (132) VaD (58) NINDS-AIREN California criteria	HR 1.4 (1.0-2.0) HR 1.6 (0.98-2.67) HR 1.8 (1.0-3.0) HR 0.8 (0.3-2.1)	Age, race, education, depression, and vascular factors
Akomolafe et al, 2006	USA, The Framingham Study, 2210 community-based subjects, 1325 (60%) women	70±7.0	12.7	Medical records Anti diabetic drugs Random blood glucose 202 (9.1%) diabetes	AD (237) DSM-IV NINCDS-ADRDA NINDS-AIREN	RR3.0 (1.1-8.4) in subjects without APOEε4 or elevated plasma Homocysteine levels	Age, sex, education, and vascular factors
Hayden et al, 2006	USA, community-based 3264 subjects, 58.2% women	65+	3.2	Medical records Self-report 343 (10.5%) diabetes	Dementia (185) DSM-III-R AD (104) NINCDS-ADRDA VaD (37) NINDS-AIREN	HR 1.6 (0.9-2.6) HR 0.9 (0.3-2.2) HR 3.3 (1.0-9.8) in women	Age, education, APOEε4, BMI, and vascular disease
Luchsinger et al, 2005	USA, 1138 Medicare recipients, 69.8% women	65+	5.5	Self-report Anti diabetic drugs 20.3% diabetes	AD(176)NINCDS-ADRDA Dementia (270) Clinical diagnosis	HR 4.8 (1.9-11.6)	Age, sex, race, education, and APOEε4
Borenstein et al, 2005	USA, The Kame Project, 1859 Japanese Americans, 55.9% women	65+	6	Self-report Anti diabetic drugs 17.2% diabetes	ADDSM-IV NINCDS-ADRDA	HR 3.3 (1.4-8.1) in ε4 non carriers	Age, gender, low income, and TIA
Whitmeret al, 2005	USA, a retrospective cohort study, 8845 participants, 53.7% women	40-44	30	Self-report Antidiabetic drugs Fasting or random blood glucose, 11.3% diabetes	Dementia (721)ICD-9	HR1.5 (1.2-1.8)	Age,sex,race,and education
Schnaider-Beeriet al, 2004	USA, a retrospective cohort study, 1892 Jewish men	40-65	35	Medical records Anti diabetic drugs OGTT 2.5% diabetes	Dementia (309) DSM-IV Hachinski's ischemic scale	OR 2.8 (1.4-5.7)	Age, sex, education, and cardiovascular disease
Xuetal, 2004	Sweden, The Kungs holmen Project, 1301 community-based dementia-free individuals, 75% women	75+	6	Medical records Anti diabetic drugs Randomblood glucose, 8.8% diabetes	Dementia (350) DMS-III-R AD (260) NINCDS-ADRDA VaD (49) NINDS-AIREN Hachinski's ischemic scale	HR 1.5 (1.0-2.1) HR 1.3 (0.9-2.1) HR 2.6 (1.2-6.1)	Age, sex, MMSE, education,and vascularfactors
Luchsinger et al, 2004	USA, a random sample of 683 Medicare recipients, 70.5% women	65+	5.4	Self-report Antidiabetic drugs 22.3% diabetes	Dementia (137) DSM-IV AD (137) NINCDS-ADRDA	HR2.2 (1.5-3.1) HR2.2 (1.6-3.2)	Age, sex and education

Table continued

Table II *(Continued)*. Major population-based prospective studies concerning the association of diabetes with dementia. The relative risk (RR), hazard ratios (HR), odds ratios (OR), or standard mortality rate (SMR) refer to dementia, when not otherwise specified.

Author, year	Country and study population	Age (y)	Follow-up (y)	Diabetes: ascertainment of cases	Dementia: N of cases and diagnostic criteria	Results	Covariates
Arvanita-kisetal, 2004	USA, 824 Catholic nuns, priests and brothers, 68.8% women	55+	9	Medical records Antidiabetic drugs 127 (15.4%) diabetes	AD(151) Clinical diagnosis	HR1.6 (1.1-2.5)	Age, sex and education
Yamada et al, 2003	Japan, a prospective study, 1774 subjects	43+	30	Medical records (no f diabetes not shown)	Dementia (114) DSM-III-R AD (51) DSM-IV VaD (38)	OR4.4 ($p = 0.007$) R1.3 ($p = 0.06$)	Age, sex and education No significance after multi-adjustment
MacKnight etal, 2002	Canada, The Canadian StudyofHealthand Aging,community-based cohort,5574subjects, 61%women	65+	5	Self-report Antidiabetic drugs Random blood glucose 503 (9.0%) diabetes	Dementia (467) CAMDEX AD (267) NINCDS-ADRDA VaD (89) NINDS-AIREN	RR1.3 (0.9-1.8) RR1.3 (0.8-2.0) RR2.0 (1.2-3.6)	Age, sex, education, andvascular disease
Peila et al, 2002	USA, The Honolulu Asia Aging Study, 2574 men (216autopsy)	72-91	3	Self-report Antidiabetic drugs Fasting or OGTT 35% diabetes	Dementia (128) DSM-II-R AD (68) NINCDS-ADRDA VaD (34) California criteria	RR1.5 (1.0-2.2) RR1.8 (1.1-2.9) RR2.3 (1.1-5.0)	Age, education, *APOE* ε4, survival status, and vascular factors and disease
Hassing et al, 2002	Sweden, a population-Based cohort, 702 individual twins (351 pairs), 70% women	80+	8	Medical records Self-report 18.5% diabetes	Dementia (187) DSM-III-R AD (105) NINCDS-ADRDA VaD (50) NINDS-AIREN	RR1.2 (0.8-1.7) RR0.8 (0.5-1.5) RR2.5 (1.4-4.8)	Age, sex, education, and vascular disease
Ott et al, 1999	The Netherlands, The Rotterdam Study, 6370 elderly, 60% women	55+	2.1	Anti-diabetic drugs Random glucose or OGTT 10.9% diabetes	Dementia (126) DSM-III-R AD (89) NINCDS-ADRDA VaD (18) NINDS-AIREN	RR1.9 (1.3-2.8) RR1.9 (1.2-3.1) RR2.0 (0.7-5.6)	Age and sex
Curb et al, 1999	USA, The Honolulu Asia Aging Study, a historical prospective study, 3774 men	45-68	25	OGTT (no f diabetes not shown)	Dementia DSM-III-R ADNINCDS-ADRDA VaD California criteria	RR1.0(0.5-2.0) RR1.5 (0.8-2.8)	Age and education (No number of cases shown)
Leibson et al, 1997	USA, a population-based historical cohort study, 1455subjects with diabetes	20+	15	Fasting blood glucose OGTT 100%diabetes	Dementia (101) DSM-III-R AD (77) Autopsy	SMR1.6 (1.3-2.1) SMR1.6(1.3-2.0)	Age and sex
Yoshitake et al, 1995	Japan, 826 community-based residents, 5 9.7% women	65+	7	Self-report 8.4% diabetes	AD (42) NINCDS-ADRDA VaD (50) NINDS-AIREN	RR2.18(0.97-4.90) RR2.8(2.6-3.0)	Age (no significant effect after multi-adjustment)
Kazman et al, 1989	USA, 488 volunteer cohort, 64% women	75-85	3.7	Medical records Anti diabetic drugs	AD (32) Neuroimaging VaD (15) Consensus	OR 0.5 (0.1-2.3)	Not reported

Table III. Major epidemiological studies concerningthe association between diabetes and post-strokedementia. There lativerisk (RR), orodds ratios (OR) referto dementia, when not other wis especified.

Author, year	Country and sample	Age (y)	Diabetes: ascertainment of cases	Dementia: N of cases and diagnostic criteria	Results	Covariates
Klimkomkowicz et al, 2006	Poland, 220 hospital-based stroke patients	67.5	Medical records, antidiabetic drugs 14.5% diabetes	Dementia (44) DSM-IV	OR 3.3 (1.2-9.0)	Not reported
Ivanetal, 2004	USA, anested case-control study, 212 stroke subjects, and 1060 controls	79.2 and 78.6	Medical records antidiabetic drugs random blood glucose 14.2% diabetes	Dementia (158) DSM-IV NINCDS-ADRDA NINDS-AIREN	25% in cases, 13% incontrols ($p < 0.001$)	Not reported
Luchsinger et al, 2001	USA, acohort study, 1262 dementia-free subjects followed for 4.3 years, 68.9% women	75.6 ± 5.9	Medical records antidiabetic drugs 20% diabetes	Post-stroke dementia (36) DSM-IV AD (157) NINCDS-ADRDA	RR 3.4 (1.7-6.9) RR 1.3 (0.8-1.9)	Sex, education, race, APOEε4 and vascular disease
Desmond et al, 2000	USA, 453 stroke patients followed for 3 months	60+	Medical records Informant-report 34.4% diabetes	Dementia (119) DSM-III-R NINDS-AIREN	OR 1.8 (1.1-3.0)	Age, sex, education, race, and stroke location
Inzitari et al,	Italy, 339 stroke patients	70-76	Antidiabetic drugs Fasting blood glucose 19.6% diabetes	Post-strokedementia (57) ICD-10 NINCDS-ADRDA	OR 1.4 (0.7-2.5)	Univariate analysis
Pohjasvaara et al, 1998	Finland, 337stroke patients, followed for 3 months	55-85	In patient register 23.7% diabetes	Dementia (107) DSM-III	22.4% and 24.4% in demented and nondemented groups, $p = 0.70$	Not reported
Censori et al, 1996	Italy, 104 stroke patients, followed for 3 months	40-79	Antidiabetic drugs fasting blood glucose 26.9% diabetes	Dementia (15), NINDS-AIREN	OR 59.4 (4.3-82.1)	Age, cognition, and infarctions
Kokmen et al, 1996	USA, 971 stroke patients, followed for 6728 person-years	50+	Medical records (nofdiabetes not shown)	Dementia (196) clinical evidence neuroimaging or autopsy	Nosignificant differences	Not reported
Tatemichi et al, 1993	USA, 251 stroke patients, followed for 3 months	60+	Self-report 35.1% diabetes	Dementia (66) DSM-III-R	OR 2.6 (1.3-5.3)	Age, education, race, and stroke history
Loeb et al, 1992	Italy, 108 stroke patients, 17.6% women, followed for 4 years	65.1	Self-report (nofdiabetes not shown)	Dementia (25) DSM-III-R	No significant differences	Not reported

Table IV. Major population-based prospective studies concerning the association of prediabetes with cognitive impairment. The odds ratios (OR) refer to cognitive decline or cognitive impairment, when not otherwise specified.

Author, year	Study population	Age (y)	Prediabetes: ascertainment of cases			
Vanhanen et al, 1997	Finland, 22 fasting blood glucose 5.9-11 mmol/l, 26 controls	65+	Fasting blood glucose 5.9-11 mmol/l (median)	Memory, attention, visuomotorspeed, verbal fluency	Subjects with glucose 5.9-11.0 mmol/l developed more associated cognitive deficits than controls	Not reported
Kalmijin et al, 1995	The Netherlands, 462 men	69-89	OGTT 47 (9.8%) prediabetes	MMSE < 26	OR1.2 (1.0-1.4)	Age,occupation, and smoking
Yaffe et al, 2006	USA, 7027 postmenopause women, followed 4 years	66	Fasting blood glucose 297 (4.6%) prediabetes	5 standard cognition tests (Z scores change < 0)	OR1.6 (1.0-2.6) for cognitive decline	Age
Vanhanen et al, 1998	Finland, 1300 subjects, followed 3.5 years	73	OGTT and fasting blood glucose 80 (6.2%) prediabetes	MMSE and 6 cognitive tests	Prediabetes was associated with mild impaired cognitive function	Age and education

betic group, which might have led to an underestimation of the disease risk attributable to diabetes. In addition, the diabetes-related cognitive deterioration may be attenuated by effective glycemic control[64,65], but studies that addressed the relation of diabetes to dementia generally did not take into account the effect of glycemic control and diabetes duration.

Third, different criteria used in the diagnosis of dementia and its subtypes can have a large impact on the frequency of dementia. Most of the longitudinal studies have used similar criteria for dementia and AD. Yet the criteria for VaD differed among the studies. These criteria are not interchangeable, with the California criteria being more sensitive but less specific than the (NINDS-AIREN) criteria[66]. Within individual studies the reliability of these diagnostic criteria will be affected by the nature of the diagnostic work-up. The diagnosis of VaD is difficult in epidemiological studies, and the boundaries between AD and VaD remain controversial[67]. Recently, a validated a set of ten lipids from peripheral blood were defined that could that predict phenoconversion to either amnestic mild cognitive impairment or Alzheimer's disease within a 2-3 year timeframe with over 90% accuracy[68]. This panel reflects cell membrane integrity, and may thus be sensitive to early neurodegeneration of preclinical Alzheimer's disease[68].

Fourth, an in-depth analysis of the modulating effect of comorbid disorders was generally not provided. Stroke, cardiovascular disease, and hypertension are known risk factors for dementia, and they should be taken into account when the relation between diabetes and dementia is examined[69-71].

Conclusions

There is an increasing interest in the scientific world towards the suggested diabetes-dementia association due to the high relevance of the topic, not only from a public health perspective, but also from a scientific point of view. In fact, exploring this association may help in clarifying some new pathways leading to neurodegeneration.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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