Can J Diabetes 41 (2017) 114–119

Contents lists available at ScienceDirect

Canadian Journal of Diabetes

journal homepage: www.canadianjournalofdiabetes.com

Review

Effects of Diabetes Mellitus on Cognitive Decline in Patients with Alzheimer Disease: A Systematic Review

Jun Li MD [a,b,*], Matteo Cesari MD, PhD [b], Fei Liu MD [c], Birong Dong MD, PhD [a], Bruno Vellas MD, PhD [b]

[a] The Center of Gerontology and Geriatrics, West China Medical School/West China Hospital, Sichuan University, Chengdu, Sichuan, China
[b] Institut du Vieillissement, Gérontopôle, Université Toulouse III-Paul Sabatier, Toulouse, France
[c] Department of Nephrology, West China Medical School/West China Hospital, Sichuan University, Chengdu, Sichuan,China

ARTICLE INFO

Article history:
Received 7 December 2015
Received in revised form
26 June 2016
Accepted 14 July 2016

Keywords:
Alzheimer disease
cognitive decline
cognitive function
diabetes mellitus
systematic review

ABSTRACT

Basic and clinical research support a link between diabetes mellitus and Alzheimer disease (AD). However, the relationship with AD progression is unclear. This review focuses on the association between diabetes and cognitive decline in patients with AD.

The literature published through May 2015 was searched in 3 databases: PubMed, Embase and Cochrane. Studies evaluating the effects of diabetes on patients with AD or cognitive decline were included, and extracted data were analyzed. A total of 10 articles met the inclusion criteria for review. The results of these studies were inconsistent in terms of the association between diabetes and cognitive decline. Only 2 studies demonstrated that the presence of diabetes was independently related to the progression of cognitive decline in the patients with AD, and 3 studies suggested that histories of diabetes were not correlated with the changes in cognitive function in patients with AD. Half of the included studies even indicated that histories of diabetes were associated with lesser declines in cognitive function in patients with AD.

Current evidence indicates that the link between diabetes and cognitive decline in patients with AD is uncertain. Further clinical studies are needed, with larger samples, long-term follow up and an extended battery of cognitive assessments.

Mots clés :
maladie d'Alzheimer
déclin cognitif
fonctionnement cognitif
diabète sucré
examen systématique

RÉSUMÉ

La recherche fondamentale et la recherche clinique établissent un lien entre le diabète sucré et la maladie d'Alzheimer (MA). Cependant, la relation avec la progression de la MA n'est pas claire. La présente revue porte sur l'association entre le diabète et le déclin cognitif chez les patients atteints de la MA.

La littérature publiée jusqu'en mai 2015 a été recherchée dans 3 banques de données : PubMed, Embase et Cochrane. Les études qui évaluent les effets du diabète sur les patients souffrant de la MA ou d'un déclin cognitif ont été choisies, puis les données extraites ont été analysées. Un total de 10 articles répondaient aux critères d'inclusion de la revue. Les résultats de ces études étaient contradictoires en fait d'association entre le diabète et le déclin cognitif. Seules 2 études démontraient que la présence du diabète était indépendamment liée à la progression du déclin cognitif chez les patients atteints de la MA, et 3 études suggéraient que les antécédents de diabète n'étaient pas corrélés avec les changements dans le fonctionnement cognitif des patients atteints de la MA. La moitié des études indiquaient même que les antécédents de diabète étaient associés à un déclin moindre du fonctionnement cognitif des patients atteints de la MA.

Les données probantes actuelles indiquent que le lien entre le diabète et le déclin cognitif chez les patients atteints de la MA est incertain. D'autres études cliniques qui comportent des échantillons de plus grande envergure, un suivi à long terme et une vaste batterie d'évaluations du fonctionnement cognitif sont nécessaires.

* Address for correspondence: Jun Li, MD, The Center of Gerontology and Geriatrics, West China Medical School/West China Hospital, Sichuan University, No. 37, GuoXue Xiang, Renmin Nan Lu, Chengdu, Sichuan 610041, China.
E-mail address: jundream2013@163.com (J. Li).

1499-2671 © 2016 Canadian Diabetes Association.
http://dx.doi.org/10.1016/j.jcjd.2016.07.003

Introduction

Age-related conditions, dementia and type 2 diabetes mellitus (diabetes) are characterized by increased incidence and prevalence with ageing and have become a major public health concern all over the world. It is estimated that 35.6 million people worldwide were living with dementia in 2010, and this number is projected nearly to double every 20 years. By 2040, the number of people with dementia is predicted to be 81.1 million worldwide (1). At the same time, dementia is the main cause of disability in older adults, thus representing a relevant burden for individuals and society as a whole. Alzheimer disease (AD) is the most common form of dementia in the elderly, and current estimates suggest that it may affect more than 24 million individuals around the world (2). On the other hand, according to the International Diabetes Federation, diabetes affects at least 382 million people worldwide, and that number is expected to reach 592 million by the year 2035 (3). This increase is particularly evident in the population older than 65 years of age. About 26% of patients over the age of 65 have diabetes (4). Older adults with diabetes also are at greater risk than other older adults for all types of dementia, including AD (5).

Mounting epidemiologic studies (6–8) and biologic evidence (9–11) support a link between diabetes and AD. Diabetes is associated with the development of cognitive impairment because of its vascular and neurodegenerative effects. As the most common neurodegenerative disorder, AD is characterized by the presence of several pathologic hallmarks, including neuronal loss, formation of senile plaques composed of extracellular deposits of amyloid beta (Abeta) in the brain. Insulin resistance, 1 of the major components of type 2 diabetes, is a known risk factor for AD (11). Insulin resistance increases Abeta generation in the brain, although the exact mechanism is unknown (9). Thus, AD and diabetes may share common cellular and molecular mechanisms. However, some study results are controversial (12–15). It remains uncertain whether diabetes promotes the progression of cognitive decline once AD is diagnosed.

The primary objective of this systematic review was to explore the cognitive decline occurring in patients with AD in relationship to the presence of diabetes.

Methods

Databases and searches

On May 20, 2015, a search without time-span limitation was performed in 3 databases: PubMed, Ovid Embase and Cochrane Central Register of Controlled Trials. According to the principles of evidence-based clinical practice, the search strategies were based on Patient, Intervention/Control, Outcome (PICO) with Medical Subject Headings (MeSH) searching terms: dementia, Alzheimer's disease, diabetes mellitus, diabetes, hyperglycemia and cognitive decline. The searches were limited to literature in English and concerning humans. There was no restriction regarding the type of publication or publication status. Additional manual searches were also conducted in order to complete the reference list, starting with the articles already identified.

Selection of studies

Search results were imported to Endnote, and duplicates were removed. Two reviewers (JL, FL) independently checked the titles and abstracts of articles for inclusion based on the following selection criteria. The full texts of the articles were retrieved if there was any doubt whether the article should be excluded or not. Disagreements were resolved by discussion, if necessary.

Inclusion criteria

To be included, articles had to meet the following 6 inclusion criteria:

1) Original clinical study, independent of its study design;
2) Enrolment with AD at 18 years of age or older, regardless of gender, disease course or disease severity;
3) Diagnosis of AD in agreement with any 1 of the following operational definitions:
   a) The International Classification of Diseases (ICD) v. 9 or 10 (ICD 1989; World Health Organization (WHO 1992);
   b) The Diagnostic and Statistical Manual of Mental Disorders (DSM) III, III-R, and IV (American Psychological Association (APA) 1980; APA 1987; APA 1994);
   c) The National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) (16);
4) Evaluation of the effect of diabetes on cognitive function in patients with AD, independent of the type of diabetes;
5) If several vascular risk factors were simultaneously assessed in a study of AD, the study was retained if it described the specific effects of diabetes on cognition;
6) One or more cognitive tests were used to assess the cognitive function modifications.

Any duration of follow up was eligible. If several papers from the same cohort/study had been published, the most complete and recent study was considered in the present review.

Exclusion criteria

Studies evaluating patients with dementia other than AD or involving participants younger than 18 years of age were not considered in the present review.

Data extraction

Data were extracted independently by 2 reviewers (JL, FL) from the included articles. Information on age and number of participants, study design, severity of AD, outcome measures on cognitive decline, duration and completeness of follow up, and conclusions drawn by authors were collected. The main limitations of each study were identified as well as its main strengths. Disagreements were resolved through discussion with a third member (BD) of the review team, if necessary.

Results

A flowchart of the search is shown in the Figure 1. A total of 1249 potentially relevant articles were retrieved by the above-described search strategy. Duplicate studies (n=223) and reviews (n=376) were excluded. Based on title and abstract screening, 622 articles were then excluded. After full-text evaluation, another 18 were found to be off topic or irrelevant for the purpose of the present review.

The inclusion criteria were met by 10 articles that included a total of 3162 patients (12–15,17–22). In other words, these patients were diagnosed as having diabetes with AD. Of the included studies, 4 were conducted in the United States (12,14,17,18); other studies were from Europe, Asia and South America (13,15,19–22). All of them were cohort studies (6 prospective cohort studies and 4 retrospective cohort studies). The number of participants ranged from 101 to 972 subjects. The ages of the participants ranged from 70 to 84 years at the baseline visits. The follow-up times ranged from 12 to 60 months. Of the studies (12,14,15,18,20,22), 6 recruited participants in the community; the other 4 studies did not provide information about the sources of the study populations.