Association between Dementia and Diabetes Mellitus: A Systematic Review
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ABSTRACT
Background: The association between diabetes mellitus and dementia is not well-established such that found between diabetes mellitus and vascular diseases. This article aimed at reviewing the longitudinal prospective studies which evaluated the association between diabetes mellitus and incidence of dementia among different age groups of patients.
Methods: An electronic search was performed by Google Scholar, PubMed, and Sciencedirect to identify all relevant articles. The number of eligible articles based on titles and abstracts were 21 eligible articles. After that, the irrelevant, duplicated and other reviews studies were excluded based on, which resulted in the exclusion of 13 irrelevant articles. Finally, 7 articles were included in this review. The data collected about mean age of the population, type and duration of diabetes, the strength of association and the statistical significance.
Results: The strength of association between dementia and diabetes mellitus varied in the included studies, the reported ratios varied from a relative risk of 1.2 to a 4.77. Regarding the statistical significance of these associations, all the studied articles revealed significant associations with P values less than 0.05.
Conclusion: This review supported the evidence of the association between diabetes mellitus and occurrence of dementia depending on the findings of the recent epidemiological studies.
Keywords: Dementia; Diabetes Mellitus; Alzheimer; Cognitive.

INTRODUCTION
Diabetes mellitus is a metabolic disease that associated with an absolute or relative shortage in insulin secretion (1). It is a growing public health problem with recent projections of an increase in international prevalence from 2.8% in 2000 to 4.4% in 2030 (2). Dementia is the severe deterioration of cognitive functions which is usually associated with old age when about a third of people above 85 years old could be affected (3). Similarly, the occurrence of diabetes mellitus increases with age to reach 15% prevalence among people above 80 years old (4).

The vascular diseases have been found responsible for adverse health effects such as cognitive impairment and dementia. However, diabetes mellitus has not similar well-established associations. Many studies, after adjustment of age effect, found that diabetes mellitus is an independent predictor for the incidence of dementia and impairment of cognitive functions (4-6). However, these studies used cross-sectional designs that characterized by an absence of the temporal relationship which should be initiated between the risk factor (diabetes mellitus) and outcome (dementia).

The longitudinal approaches are more appropriate to study the presence and magnitude of such association (7). In a longitudinal study conducted by Whitmer et al. (8). Patients with a history of major hypoglycemic shocks were at a higher risk of dementia. Another longitudinal study reported a strong relationship between diabetes mellitus and dementia related to the incidence of stroke with lower risk in Whites than in Blacks (9). A study reported twofold elevated risk of dementia among patients with diabetes mellitus (10). The reported cognitive decrements including verbal, memory, and information processing ability.

However, the limited psychometric screening and inaccurate cognitive function tests reduced the confidence on the findings of these studies. This article aimed at reviewing the longitudinal prospective studies which evaluated the association between diabetes mellitus and incidence of dementia among different age groups of patients.

METHODS
Keywords and search strategy
The keywords and search strategy used in this review were showed in the summary of search findings (table 1). All steps of the systematic review (identification, screening, eligibility, inclusion) were conducted in this review.

Eligibility Criteria
All articles published in English language and published in the last decade (since 2006) were
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eligible to be included in this review. The number of eligible articles based on titles and abstracts was 21 eligible articles. After that, the irrelevant, duplicated and other reviews studies were excluded based on, which resulted in the exclusion of 13 irrelevant articles. Finally, 7 articles were included in this review.

Data Sources
An electronic search was performed by Google Scholar, PubMed, and Science direct search engines using Boolean operators. The search strategy used here was demonstrated in the table (1).

Data Extraction
To ensure that, the extraction of all required information in regard to the association between diabetes mellitus and dementia was done, two reviewers conducted the searching and screening of the eligible articles.

The data were collected in data extraction form shown in table (2), including the following:

- Study design
- Sample size
- Age group of the patients
- Type of diabetes mellitus
- The duration of diabetes mellitus
- Type of psychomotor screening tests
- Type of cognitive function tests
- The odds ratio and relative risk of the associations
- The statistical significance of the association

The study was done after approval of ethical board of Jazan university.

RESULTS

The search of the literature, after exclusion of irrelevant, duplicated and review studies revealed 7 studies which met the inclusion criteria. Included studies aimed at comparing the Association between dementia and diabetes mellitus. The sample size of included studies ranged from 104 cases in a study conducted by Plastino et al.\(^{(11)}\) to more than two million persons representing people registered in Danish psychiatric registration \(^{(12)}\). The mean age association between dementia and diabetes mellitus of participants ranged from 64.2 years in the study conducted by Lin et al.\(^{(13)}\) to 85 years in a study conducted by Ahtiluoto et al.\(^{(14)}\).

In relation to the type of diabetes, the following studies reported include type I & type II diabetes among their participants \(^{(15, 13)}\). Three studies reported only type II diabetes among their participants \(^{(11, 16, 17)}\). Regarding the type of psychomotor screening tests, only one study conducted by \(^{(12)}\) reported using data from the Danish Psychiatric Central Research Register.

Concerning the type of cognitive function tests used, four studies reported positively, the Diagnostic and Statistical Manual of Mental Disorders criteria (DSM) was used as a tool in research study \(^{(15)}\) which reported using the 3\(^{rd}\) or 4\(^{th}\) edition. Lin et al.\(^{(13)}\) reported inpatient and outpatient databases relied on the ICD-9-CM (International Classification of Diseases, Ninth Revision, and Clinical Modification).

Plastino et al.\(^{(11)}\) utilized the Mini Mental State Examination (MMSE), while the Clinician's Global Impression (CGI), were utilized by another study conducted by Ahtiluoto et al.\(^{(14)}\) where assessment based on data obtained from interviews, health examinations, previous health and social work records, and tests of cognitive functions and functional capacity.

The strength of association between dementia and diabetes mellitus varied in 7 studies, where the reported ratios varied from a relative risk of 1.2 in the study carried out by Katon et al.\(^{(12)}\) to a 4.77 in a study conducted by Akomolafe et al.\(^{(15)}\).

Regarding the statistical significance of these associations, all studies found significant associations with P values were less than 0.05 \(^{(11-18)}\). Other important outcomes were only noted in a study carried out by Chatterjee et al.\(^{(17)}\) stating that women with diabetes had a 19% greater risk for the development of vascular dementia than men.
Table (1): Summary of search results

<table>
<thead>
<tr>
<th>Search Engine</th>
<th>Search Terms</th>
<th>Papers</th>
<th>Titles of the eligible articles based on the title and abstracts</th>
<th>Excluded</th>
<th>Included</th>
</tr>
</thead>
<tbody>
<tr>
<td>Google Scholar</td>
<td>Dementia and diabetes mellitus (2007-2017)</td>
<td>34000</td>
<td>9 eligible studies</td>
<td>3 reviews + 2 irrelevant study + 2 duplicated</td>
<td>2 studies included</td>
</tr>
<tr>
<td>PubMed</td>
<td>Dementia and diabetes mellitus (2007-2017) (human studies)</td>
<td>1641</td>
<td>10 eligible studies</td>
<td>4 duplicated + 3 reviews</td>
<td>3 included</td>
</tr>
<tr>
<td>Science Direct</td>
<td>Dementia and diabetes mellitus (2007-2017) (Only journals)</td>
<td>7515</td>
<td>2 eligible studies</td>
<td>-</td>
<td>2 studies included</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>43156</td>
<td>21 eligible studies</td>
<td>14 excluded studies</td>
<td>7 included studies</td>
<td></td>
</tr>
</tbody>
</table>

Table (2): Summary of the findings

<table>
<thead>
<tr>
<th>Study Citation (Author-Year)</th>
<th>Study design</th>
<th>Sample size</th>
<th>Mean age group of the patients</th>
<th>Type of diabetes mellitus</th>
<th>Mean duration of diabetes mellitus</th>
<th>Type of psycho-motor screening tests</th>
<th>Type of cognitive function tests</th>
<th>The measures of the association between dementia and D.M.</th>
<th>The statistical significance of the association</th>
</tr>
</thead>
<tbody>
<tr>
<td>[14]</td>
<td>a population-based neuropathologic study</td>
<td>553 individuals</td>
<td>85</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>interviews, health examinations, previous health and social work records, and tests of cognitive function and functional capacity</td>
<td>1.77 (1.14–2.74)</td>
<td>At baseline= 0.074 At death= 0.381</td>
</tr>
<tr>
<td>[19]</td>
<td>prospective cohort study</td>
<td>3075 community dwelling older adults of white and black race/ethnicity</td>
<td>74.0 years</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>determined by the date of the first available record of a dementia diagnosis</td>
<td>2.2; 95% CI, 1.1-4.6)</td>
<td>P &lt; .03</td>
</tr>
<tr>
<td>[12]</td>
<td>a national population-based cohort study</td>
<td>2454 532 adults</td>
<td>65 years old</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>using data from the Danish Psychiatric Central Research Register</td>
<td>1.20 (95% CI, 1.17-1.23)</td>
<td>(P &lt; .001) for those younger than 65 years. (P = .001) for those 65 years or older.</td>
</tr>
<tr>
<td>[11]</td>
<td>prospective, open-label, observational study</td>
<td>104 patients</td>
<td>76.2±16.4 years</td>
<td>diabetes Mellitus type-2</td>
<td>Not reported</td>
<td>Not reported</td>
<td>using data from the Danish Psychiatric Central Research Register</td>
<td>1.20 (95% CI, 1.17-1.23)</td>
<td>(P&lt;.001). For both (MMSE) AND (CGI)</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Sample Size</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Global Impression (CGI)</th>
<th>and DM</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>[16]</td>
<td>a cross-sectional</td>
<td>8213 subjects Among all of these, 1,109 subjects with T2DM</td>
<td>65 years</td>
<td>type 2 diabetes mellitus</td>
<td>Not reported</td>
<td>Not reported</td>
<td>DSM-IV criteria</td>
</tr>
<tr>
<td>[15]</td>
<td>a prospective community-based cohort study</td>
<td>2210 persons</td>
<td>70 years</td>
<td>both type 1 DM and type 2 DM</td>
<td>Not reported</td>
<td>Not reported</td>
<td>diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria</td>
</tr>
<tr>
<td>[13]</td>
<td>7-year follow-up study</td>
<td>a total of 15,404 diabetic subjects</td>
<td>64.2 years</td>
<td>both</td>
<td>Not reported</td>
<td>Not reported</td>
<td>inpatient and outpatient databases based on ICD-9-CM diagnostic codes</td>
</tr>
</tbody>
</table>
DISCUSSION

In this review, the association between dementia and diabetes mellitus was examined. The results showed that the factors in consideration being the patients' age and type of diabetes mellitus. Both types of diabetes mellitus were associated with the decrement of cognitive function but the association was most consistent for type 2 diabetes and older patients. This included studies with higher means of age showed a tendency to report a higher association between dementia and diabetes mellitus in patients (14, 15, 19).

The majority of included studies were prospective epidemiological studies (11-13, 15, 19), while the remaining two studies were large-scale population-based surveys (14, 16).

The most important findings among all included studies were the reporting of significant associations between dementia and diabetes mellitus in different age groups and different populations. They differed only in the strength of these associations, assessed by odds ratio and relative risks. The strength of this association varied from a 1.2 in the study (12) carried out by Katon et al. to a 4.8 in another study conducted Akomolafe et al. (15).

Evidence gathered from the included studies revealed that diabetes mellitus is an important risk factor for incidence of dementia, which is usually associated with a progressive deterioration of cognitive skills (20). In another hand, the decline in cognitive skills can result in inadequate self-control of blood glucose, which leads to more complications accompanied with episodes of hyper- and hypoglycemia (21). The study of Lin and Shen showed that the patients suffered more frequently to hypoglycemic episodes are linked to stronger association with dementia than those without. The included studies showed that the association between dementia and diabetes mellitus seems to be more related to the occurrence of hypoglycemic episodes rather than to the type of diabetes mellitus.

The relationship linked dementia to diabetes mellitus act as a positive feedback cycle where uncontrolled blood glucose increase incidence of dementia, and in turn dementia can result in poor self-management of diabetic patients due to deterioration of cognitive functions. Thus, poor management of blood glucose can be considered the main risk factor for the development of dementia in diabetic patients (22).

CONCLUSION

This review supported the evidence of the association between diabetes mellitus and occurrence of dementia based on the findings of recent epidemiological studies.

Conflict of interests

The authors declared that no financial support was provided and no conflict of interests

REFERENCES


