

**Revisión**

# Thinking sweet: the relationship between diabetes and cognitive dysfunction

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**Abstract**

With the aging of the population the prevalence of two common disorders is expected to rise: diabetes and dementia. It has been shown that people with diabetes are approximately 1.5 times more likely to experience cognitive decline and 1.6 more likely to develop frank dementia than people without diabetes. This appears to be due to a higher prevalence of both vascular dementia and Alzheimer's disease. The aim of this review is to describe the importance of this relationship, the evidence supporting it, possible explanations, and the implications of this relationship for physicians caring for people with diabetes.

**Keywords:** diabetes, dysglycemia, cognitive dysfunction, dementia.

**Introduction**

With the aging of the population the prevalence of two common disorders is expected to rise: diabetes and dementia. It has been shown that people with diabetes are approximately 1.5 times more likely to experience cognitive decline and 1.6 more likely to develop frank dementia than people without diabetes.<sup>1</sup> This appears to be due to a higher prevalence of both vascular dementia<sup>2-5</sup> and Alzheimer's disease.<sup>2-7</sup>

This overview will describe the growing importance of diabetes, dementia and cognitive dysfunction in an aging society. It will describe the epidemiological data supporting the relationship between these entities and the existence of a disorder that may be labeled "diabetes related cognitive dysfunction". It will then go on to describe proposed pathophysiological mechanisms responsible for this relationship and elaborate on data supporting the role of dysglycemia in the development of cognitive dysfunction. Finally, it will present the possible clinical implications of this association to physicians treating older people with diabetes.

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**List of acronyms quoted in the text:**

CV: cardiovascular; CVD: cardiovascular disease; IFG: impaired fasting glucose; IGT: impaired glucose tolerance.

**The importance of the link between cognitive dysfunction, dementia and diabetes: prevalence data**

The prevalence of dementia is anticipated to rise because of the increase in older members of the population. For example, the Canadian Study of Health and Aging reported that the prevalence of dementia was 8% for people over 65 and 34% for those aged 85 or older.<sup>4</sup> Similarly, a pooled analysis of 11 European studies reported an age-standardized dementia prevalence rate of 6.4%; rising in those over 90 to 28.5%.<sup>8</sup> In a recent study from the US it was projected that the number of people with Alzheimer's disease, the most common form of dementia, will triple from 4.5 million in 2000 to 13.2 million by 2050.<sup>9</sup>

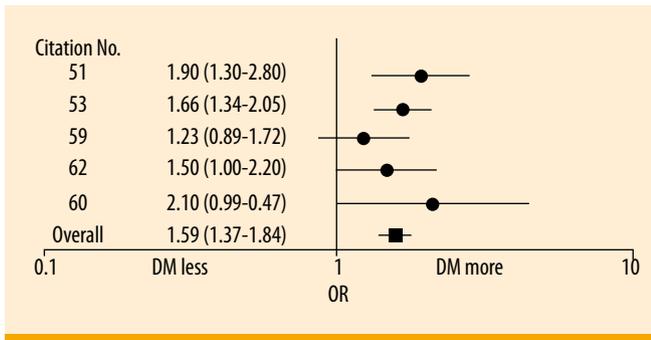
Preceding the onset of dementia is a long period of cognitive decline thus cognitive dysfunction represents an important phase on the path (of cognitive decline) from normal cognitive function to dementia. The prevalence of this state (pre dementia) is also expected to rise with the aging of the population. For example, the Cardiovascular Health Study (age over 65) reported a pre dementia (i.e. minimal cognitive impairment) prevalence of 19% overall; and 29% in those over age 85.<sup>10</sup>

The prevalence of diabetes is also expected to rise with the aging of the population thus the global prevalence of established diabetes was estimated to be 2.8% in 2000 and is projected to be 4.4% by 2030.<sup>11</sup> Over the past 20 years several studies have indicated that diabetes particularly type 2 diabetes is associated with an increased risk for cognitive dysfunction and dementia.<sup>1,3-6,12-23</sup>

The prevalence rates described, combined with the long duration of these disorders, the anticipated economic burden on society and the associated deficits in self care ability highlight the importance of a better understanding of these disorders and the mechanisms that may entwine them.

**Epidemiological evidence supporting a relationship between diabetes cognitive dysfunction and dementia**

Type 2 diabetes is a metabolic disorder characterized by hyperglycemia that is caused by a relative lack of insulin i.e. insufficient amount, activity ("insulin resistance") or both and is associated with a high risk of serious chronic diseases. It is well established as an independent risk factor for eye, kidney and neurological diseases as well as for cardiovascular morbidity and mortality.



**Figure 1.** Risk for dementia diabetes vs no diabetes

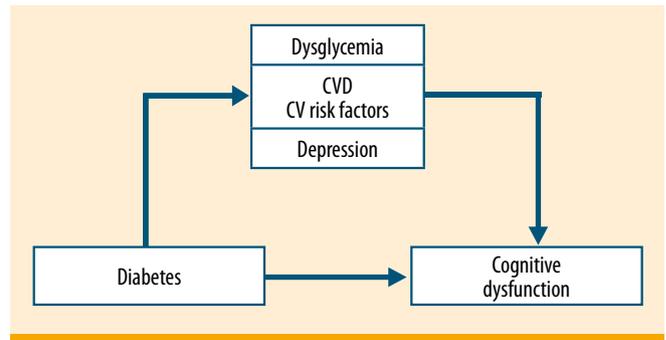
A systematic review of prospective observational studies demonstrated that people with diabetes also have a greater risk for an accelerated rate of cognitive decline and progression to dementia. In a follow-up duration of 2-18 years this review showed that people with diabetes (n= 8,656) when compared to those without diabetes: a) had a greater rate of decline in cognitive function; b) a 1.5 fold greater risk of cognitive decline; and c) a 1.6 fold greater risk for future dementia.<sup>24</sup> Perhaps, as anticipated, given the relationship between diabetes and cardiovascular disease, people with diabetes had a 2.2-3.4 greater risk for the development of vascular dementia. However, interestingly people with diabetes also had a 1.2-2.3 greater risk for the development of Alzheimer’s dementia.

Prospective studies with longer follow-up periods strengthen these observations. The Adult Health Study followed a cohort of atomic bomb survivors from Hiroshima and Nagasaki. After 34 to 39 years of follow up, 1,774 participants were screened for dementia. Compared to non diabetic individuals, diabetes increased the risk for vascular dementia and Alzheimer’s dementia 1.3 and 4.4 fold respectively.<sup>25</sup> The Israel Ischemic Heart Disease (IIHD) study showed that people with a diagnosis of diabetes in midlife had a 2.83 greater risk for the development of dementia 3 decades later compared to individuals without diabetes.<sup>26</sup>

Taken together the results of these studies strengthen the conclusion that indeed cognitive dysfunction should be considered as yet another chronic consequence of diabetes that may be termed: “diabetes related cognitive dysfunction” (figure 1).

### Possible explanations for the relationship between diabetes and cognitive dysfunction

A number of possibilities may explain the relationship between diabetes and cognitive dysfunction. First, diabetes is well established as a risk factor for cerebrovascular disease; it is also associated with hypertension and dyslipidemia. Thus, a relationship between cognitive dysfunction and diabetes may be mediated through cerebrovascular disease and this may be more pronounced in the older age group. Second, depression occurs more frequently in people with diabetes and is difficult to differentiate clinically from dementia and early cognitive decline. These two may explain part of the relationship however in many of the studies the association persisted after adjusting for CV disease, CV



**Figure 2.** Possible mediators in the diabetes cognitive dysfunction relationship

risk factors<sup>16,22</sup> and depression<sup>16,20</sup>. Third, hypoglycemia may affect cognitive function. However, in contrast to the acute negative effect of hypoglycemia on cognition, there is little evidence to support chronic cognitive impairment secondary to hypoglycemia. Indeed, intensive treatment regimens that were associated with increased hypoglycemic episodes in individuals with type 1 diabetes did not affect cognition adversely.<sup>27,28</sup> Finally, dysglycemia and chronic hyperglycemia may also contribute to cognitive dysfunction (figure 2).

### Data supporting the relationship between dysglycemia, chronic hyperglycemia and cognitive dysfunction

Data supporting this explanation come mainly from cross sectional studies. In a cross-sectional analysis of 378 high-functioning individuals with diabetes, higher A<sub>1c</sub> levels (a measure of glucose control over 6 weeks often used in people with diabetes) were consistently associated with lower scores on two cognitive tests.<sup>29</sup> Another cross sectional analysis of approximately 3,000 individuals with established type 2 diabetes (participating in the MIND-ACCORD sub-study) demonstrated an age-adjusted inverse relationship between cognitive function and the degree of chronic hyperglycemia as measured by the A<sub>1c</sub> level.<sup>30</sup>

Data from people without diabetes demonstrated a similar relationship. For example the ONTARGET/TRANSCEND cognitive baseline analysis showed that in ~20,000 individuals without diabetes there was an association between higher levels of fasting plasma glucose (FPG) levels and cognitive function as assessed by the Mini-Mental State Examination (MMSE).<sup>31</sup> ORIGIN cognitive baseline analysis demonstrated that after adjustment for age, education, CVD and CV risk factors individuals with pre-diabetes (IFG/IGT) had significantly higher cognitive scores than those with overt diabetes, suggesting that an accelerated rate of cognitive decline occurs in the transition phase from pre-diabetes to diabetes.<sup>32</sup> All these analysis were cross sectional limiting the ability to make any temporal or causal inferences regarding this relationship.

There are several prospective studies that have compared different categorizes of dysglycemia: diabetes, pre-diabetes states such as impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) with relation to the level of cognitive decline expe-

rienced. These studies have shown that people with pre-diabetes when compared with those who were normoglycemic were at increased risk of cognitive decline.<sup>20,33</sup>

### Possible explanations for the dysglycemia-cognitive dysfunction relationship

A number of possibilities may explain the association between dysglycemia, hyperglycemia and cognitive dysfunction. As higher glucose levels are associated with a higher prevalence of CV risk factors and cardiovascular disease, the relationship with cognitive dysfunction may be mediated through CV disease. However, in all the analysis described above the relationship was not attenuated by adjusting for risk factors or CV disease.

It is also possible that chronic exposure of the brain to high levels of glucose may accelerate cognitive decline. Indeed, post mortem studies from the brains of people with Alzheimer's disease demonstrate metabolic oxidation products associated with hyperglycemia.<sup>34,35</sup> A recent study in older individuals demonstrated an inverse relationship between glucose levels and function of the dentate gyrus, an area of the brain thought to be important in age related cognitive decline.<sup>36</sup>

Third, dysglycemia and higher A<sub>1c</sub> levels imply insufficient action or effect of insulin due to insufficient secretion, activity or both. There are many insulin receptors in the brain. Some have a role in glucose transport but many are thought to have a function in cognitive processes.<sup>37</sup> Several observations suggest that cognitive decline is a consequence of insufficient insulin action in the brain. Thus: a) in individuals without diabetes, worse glucoregulation (as measured by a glucose tolerance test) was associated with worse outcomes on cognitive assessment, especially in the elderly;<sup>38</sup> b) individuals with Alzheimer's disease have less efficient glucoregulation than unaffected individuals;<sup>39</sup> c) exposure of individuals with Alzheimer's disease to a hyperinsulinemic euglycemic clamp improved cognitive function whereas exposure to an euinsulinemic hyperglycemic clamp had no effect.<sup>38-41</sup>

Finally, microvascular disease may also be responsible for the deleterious effects of chronic hyperglycemia on cognitive function. Microvascular disease has been demonstrated to be worsened by chronic hyperglycemia.<sup>42,45</sup> In people with diabetes it causes pathology in the retina and in the peripheral nervous system. Thus, it may well be that microvascular disease occurs also in the brain resulting in cognitive dysfunction.

### The implications of "diabetes related cognitive dysfunction" to the treating physician

Diabetes and glucose control require complex self care process, indeed self-management support is established as an evidence-based intervention for diabetes.<sup>44</sup> From a patient perspective the challenges associated with having diabetes are dynamic and change over time emphasizing the need to have skills to cope with emerging situations rather than sticking to a certain regimen. Indeed a substantial amount of research supports the importance of effective problem solving for successful adjustment and coping.<sup>45</sup>

### Practical considerations

- Cognitive dysfunction should be considered as yet another chronic consequence and disabling manifestation of diabetes. People with diabetes are approximately 1.5 times more likely to experience cognitive decline and 1.6 more likely to develop frank dementia than people without diabetes. This appears to be due to a higher prevalence of both vascular dementia and Alzheimer's disease.
- Dysglycemia and chronic hyperglycemia may have a role in the pathogenesis of this phenomenon.
- Cognitive assessment should be part of clinical and research assessment of people with diabetes in order to identify those individuals with "diabetes related cognitive dysfunction" as cognitive impairment may impede self-care capacity.

One of the important determinants of effective problem solving capacity is intact cognitive function. However, as demonstrated above, cognitive dysfunction is a complication of diabetes.

The first step in treating any disease or a condition is identifying it, diagnosing or measuring it. Thus, it is important that physicians who care for people with diabetes, especially in the older age group be aware of this complication. Early recognition of cognitive impairment in elderly people with diabetes has a two-fold function. First, it may explain the incapacity to care for the disease and control glucose levels and aid the treating physician in tailoring an appropriate treatment regimen. Second, as diabetes is associated with an accelerated rate of cognitive decline, identifying cognitive impairment may be a first step in delaying its progression and possibly delaying the occurrence of dementia in this high risk population.

### Conclusions

Cognitive dysfunction should be considered as yet another chronic consequence and disabling manifestation of diabetes. Dysglycemia and chronic hyperglycemia may have a role in the pathogenesis of this phenomenon. Cognitive assessment should be part of clinical and research assessment of people with diabetes in order to identify those individuals with "diabetes related cognitive dysfunction" as cognitive impairment may impede self-care capacity. Future studies are needed in order to better characterize those individuals with diabetes more prone to progression to dementia in order to better characterize the pathophysiological mechanisms responsible for this relationship. These types of studies may broaden our knowledge and set the stage for interventions aimed at prevention/delay of the onset of dementia in people with diabetes. ■

### Potential conflicts of interest

The autor has no potential conflicts of interest regarding the content of the manuscript.

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