CHAPTER 33

NEUROCOGNITIVE DYSFUNCTION IN OLD DIABETES:

Management and Treatment

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Abstract: Type 2 diabetes mellitus (T2DM) is a risk factor for cognitive decline. However, the etiology of dementia and cognitive impairment in people with T2DM is probably multifactorial, and the precise underlying mechanism remains unclear.

Good metabolic control in elderly subjects with T2DM may contribute to prevention of the development and/or progression of cognitive decline in elderly diabetic subjects, but hypoglycemia must be avoided. Appropriate well-balanced glycaemic control should be provided to diabetic subjects with cognitive impairment.

Demented diabetic patients tend to lose self-caring ability, and behavioural and psychological symptoms of dementia (BPSD) and depressive mood; the symptoms often associated with dementia, make the management of diabetes complicated and difficult. Considering the progressive aging world-wide, more research to investigate the association between T2DM and dementia process, as well as the best way to manage this population, will be important.

INTRODUCTION

Recent evidence has indicated that Type 2 diabetes mellitus (T2DM) in the elderly is a risk factor for cognitive dysfunction or dementia. Recent studies suggest that good metabolic control in elderly subjects with T2DM may contribute to prevention of the development and /or progression of cognitive decline in elderly diabetic subjects. On the other hand, diabetic subjects with cognitive dysfunction results in restricted self-management and use of care services, which may have negative impacts on metabolic control. Comprehensive management should be warranted in diabetic elderly.

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EPIDEMIOLOGY OF COGNITIVE DYSFUNCTION IN OLD DIABETIC PATIENTS

The prevalence of T2DM increases with age, and dementia also increases its incidence in later life. Therefore, the co-incidence of T2DM and dementia increases with ageing. Recent studies have indicated that older people with T2DM have a higher risk of cognitive dysfunction or dementia.[1] There is ample evidence that T2DM is related not only to vascular dementia but also to clinical diagnosis of Alzheimer's disease (AD)-type dementia.[2]

In a large epidemiological study, The Rotterdam Study,[3] T2DM showed an increased risk for developing dementia. The study showed that patients treated with insulin were at 4.3-fold higher relative risk for dementia. Another, the Religious Orders Study,[4] which observed some 800 nuns and priests longitudinally for 9 years, showed a 65% increased risk for developing AD. The Honolulu Asia Aging Study, a cohort of Japanese Americans in Hawaii[5,6] showed a 1.8-fold higher risk for developing AD and 2.3-fold risk for vascular dementia. Numerous studies have suggested that diabetes, and in particular T2DM, is associated with an increased risk of cognitive impairment and dementia.[7,8] Recent systematic review of large prospective trials reported that T2DM increased the risk of AD as a ratio of 1.59 (range 1.15-2.7).[9] Another systematic review reported that T2DM has a risk for vascular dementia of 2.0 to 4.2.[10]

ETIOLOGY OF DIABETES-ASSOCIATED COGNITIVE DYSFUNCTION

Evidence for a connection between T2DM and AD is based upon a variety of diverse studies, but definitive underlying biochemical mechanisms remain to be elucidated. The etiology of dementia and cognitive impairment in people with T2DM is probably multifactorial. Among them the effects of chronic hyperglycemia are implicated, perhaps through several mechanisms, including promoting the development of cerebral microvascular disease.[11] Insulin resistance, which is often associated with T2DM, may be involved in the neurodegenerative process.[12] Data suggest that the brains of older people with T2DM might be vulnerable to the effects of recurrent, severe hypoglycemia.[13] Other possible moderators of cognitive function include inflammatory mediators, rheological factors, and dysregulation of the hypothalamic-pituitary-adrenal axis.[14]

Appropriate treatment of diabetes could contribute to the prevention of developing dementia. Cognitive function should now be included as a standard end point in randomized trials of therapeutic interventions in patients with T2DM.

ASSESSMENT OF DIABETES-ASSOCIATED COGNITIVE DYSFUNCTION

To screen subjects with cognitive impairment, several neuropsychological assessment tools may be applied. The mini mental state examination (MMSE) is an assessment scale for global cognition including orientation, memory, calculation, verbal ability, and constructional disabilility.[15] A full score is 30, and a cut-off point of 23/24 is usually used for the screening of dementia. The MMSE subset analysis identified impaired attention and calculation as a specific characteristic of DMs,[16] whereas patients with AD had lower scores in temporal orientation and recall.[17]

According to the systemic review by van den Berg et al, which included analysis of 27 studies,[18] the association between diabetes and cognition differed across the individual domains: processing speed was significantly affected in 63% of studies assessing that domain, attention in 50%, memory in 44%, cognitive flexibility in 38%, language in 33%, general intelligence in 31%, and perception and construction in 22% of the studies. Therefore, assessment of cognitive speed may provide early detection of diabetes-related cognitive decline. The digit symbol substitution test (DSST) is a test of cognitive speed, which can be performed relatively easily. It consists of (e.g., nine) digit-symbol pairs (followed by a list of digits). Under each digit the subject should write down the corresponding symbol as fast as possible. The number of correct symbols within the allowed time (e.g., 90 or 120 sec) is measured.

TREATMENT AND MANAGEMENT OF DIABETIC PATIENTS WITH COGNITIVE IMPAIRMENT

Glycemic Control in Diabetic Patients with Cognitive Impairment

A large cohort study, the ACCORD-MIND trail, has found that HbA1c levels were cross-sectionally associated with worse performance on several cognitive functional tests.[19] Several prospective studies[20-23] have indicated that higher HbA1c levels at baseline are associated with cognitive decline. A recent prospective study by van den Berg et al, however, showed that $HbA1_C$ levels at baseline had no effects on cognitive function.[22]

There are indications that modest cognitive decrements in patients with T2DM are partially reversible with improvement of glycemic control,[24-29] though not invariably.[30] A randomised trial comparing the effects of rosiglitazone to glyburide therapy found statistically significant cognitive improvement in both treatment groups on measures of working memory, but not on learning and cognitive speed.[28] These studies suggested that metabolic control may have beneficial effects in terms of cognitive function. On the other hand, a recent report has suggested that a history of severe hypoglycemic episodes is associated with a greater risk of dementia.[13] The diabetic control should be balanced between the merits of treatment and the risk of hypoglycemia.

The American diabetes association provides the following clinical guidance: For patients with advanced diabetes complications, life-limiting comorbid illness, or substantial cognitive or functional impairment, it is reasonable to set less intensive glycaemic target goals. These patients are less likely to benefit from reducing the risk of microvascular complications and more likely to suffer serious adverse effects from hypoglycemia. However, patients with poorly controlled diabetes may be subject to acute complications of diabetes, including dehydration, poor wound healing, and hyperglycemic hyperosmolar coma. Glycemic goals at a minimum should avoid these consequences.[31]

Good metabolic control may contribute in preventing the development and/or progression of cognitive decline in elderly diabetic subjects; however, hypoglycemia must be avoided. The appropriate well-balanced glycemic control should be provided to diabetic subjects with cognitive impairment.

Care in Diabetic Patients with Cognitive Impairment

Patients with cognitive decline may lose the ability of self-care. Cognitive dysfunction can occur in older subjects with diabetes mellitus, resulting in an impact on diabetes self-management and use of care services.[32]

Cognitive dysfunction is associated with changes in self-care behavior and the use of both health and social services. In addition, physical function is often more compromised in those with cognitive impairment. Individuals with diabetes mellitus with cognitive impairment may have difficulties performing daily tasks of diabetes mellitus self-care effectively, which may result in worse glycemic control than in those without cognitive impairment. The relationship between cognition and self-management ability may be bidirectional. While it could be that poor self-management practices lead to poorer metabolic control and therefore brain dysfunction, cognitive deterioration would lead to changes in self-management ability. The importance of patient education and compliance with therapy to foster successful diabetes management is generally recognized among diabetes health professionals[33] but this process is jeopardized by the presence of cognitive impairment. Self-management is often regarded as a set of skilled behaviors used to manage self-illness[34] but this approach places a great responsibility on the individual for their own care, a situation that is severely compromised in those with cognitive dysfunction. In these situations, it is not surprising that the need for informal caretakers increases.

A depressive mood is often comorbid with dementia,[35] especially in diabetics.[36] Depressed mood may also be associated with cognitive impairment and may interfere with effective self-management.[37-40] There is also a danger that subjects with cognitive deficit may be at risk of receiving inappropriate care (probably less aggressive therapy) by attending health professionals. Demented elderly individuals may have higher glycaemic levels because they have less intensive treatment goals.[41]

People with dementia often experience behavioral and psychological symptoms of dementia (BPSD) during the course of their illness. The management of dementia is complicated by BPSD such as psychosis, depression, agitation, aggression and disinhibition (i.e., unrestrained behavior resulting from a lessening or loss of inhibitions or a disregard of cultural constraints). BPSD is an umbrella term for a heterogeneous group of noncognitive symptoms that are almost ubiquitous in dementia. BPSD also disrupts the daily diabetes care routine, with 'denial' of having diabetes or memory loss (anosognosia) being the most disruptive.[42] Caregivers often report that caring for both diabetes and dementia is highly burdensome, that they feel overwhelmed by BPSD and that they want more support from family and patients' healthcare providers. This makes the care of demented patients with DM difficult.

To control BPSD, antipsychotic medication is sometimes prescribed. Antipsychotic drugs, especially second-generation drugs including olanzapine and quetiapine have the potential to induce weight gain and elevate plasma glucose levels.[43] The use of these drugs in demented diabetic patients should be avoided.

T2DM and dementia including AD have a possible shared pathophysiology. Management of diabetic patients with dementia is challenging and has many unsolved issues. Considering the progressive aging worldwide, it will be important to carry out investigations to better our understanding of the association between T2DM and the dementia process, and the best way of managing these populations.

CONCLUSION

T2DM and dementia including AD have a possible shared pathophysiology. Management of diabetic patients with dementia is challenging and has many unsolved issues. Considering the progressive aging worldwide, it will be important to carry out investigations to better our understanding of the association between T2DM and the dementia process, and the best way of managing these populations.

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