TYPE 2 DIABETES AND COGNITIVE IMPAIRMENT: A POTENTIAL LINKAGE AND IMPACT FOR DIABETES SELF-CARE

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ABSTRACT: For successful diabetes self-management, individuals must commit to lifelong daily self-care tasks such as adhering to diet, exercise, and medication regimens and checking blood glucose. The coordination of these tasks often requires complex cognitive functioning. Diabetes is more likely to be associated with poorly controlled blood sugar, which can damage vessels in the brain and lead to cognitive impairment. Despite the level of blood sugar, there are some potential factors that may evolve to cognitive impairment in type 2 diabetes. The purpose of this article is to present a review of the literature regarding potential factors of cognitive impairment in type 2 diabetes. Cognitive impairment in type 2 diabetes could be attributed to a variety of potential factors, including age, duration of diabetes, obesity, diabetic complications, diabetic treatment, advanced glycation end products (AGEs), glycaemic control, cardiovascular problems, inflammation and depression. Particularly, the co-occurrence of cognitive impairment and depressive mood has an impact on diabetic self-care management. Although cognitive decline and depression are common found in older people, it is often overlooked. Considering and routine monitoring of cognitive function and depressive mood in older patients with type 2 diabetic can ultimately lead to improvements in the long-term outcomes of self-care diabetes.

Keywords: Type 2 diabetes, Cognitive impairment, Depressive mood, Diabetes self-care

INTRODUCTION

Type 2 diabetes in adults is a global health issue. Around 90% of people with diabetes around the world are type 2 [1]. It has been estimated that the number of people with diabetes worldwide was 285 million in 2010 and will increase to 439 million by 2030 [2]. More than 80% of people with diabetes live in low and middle-income countries [1]. Each year more than 3.96 million people worldwide die from diabetes and its complications [3]. The prevalence of type 2 diabetes increases with age [4]. Research has linked the disease to cognitive impairment in older people [5, 6]. Recent evidence from epidemiological studies suggests that type 2 diabetes is a risk factor for cognitive impairment and dementia, both the vascular dementia (VaD) and Alzheimer's disease (AD), the two most common forms of dementia [7-10]. Older individuals (aged 60-80) with type 2 diabetes are associated with approximately a 1.5 fold level of risk of cognitive impairment compared to the same age group without type 2 diabetes [11]. Given the potential for cognitive problems to interfere with attempts to diabetes self-care management and following a physician's recommendation, cognitive decline among older people with diabetes could lead to further decline in health [12].

In Thailand, Type 2 diabetes is one of the main chronic diseases which cause a health problem in Thai older people and the numbers of older people are expected to increase over the next few decades due to the growing of ageing population [13]. In addition, a high prevalence rate (6.7%) of diabetes in Thailand makes it among the top ten in Asia [14]. Moreover, the hospitalisation rate for diabetes in Thailand has increased and shown a rising trend. For example, the hospitalisation rate for diabetes has nearly doubled over 3 years from 380.7 (x 100,000 population) in 2003 to 586.8 (x 100,000

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population) in 2006 [13]. This study intends to raise awareness of cognitive impairment and depressive mood in older people with type 2 diabetes.

DEFINITION OF COGNITIVE IMPAIRMENT

Cognitive impairment is a defining feature of dementia. Dementia is characterized by the development of multiple cognitive deficits that include memory impairment and at least one of the following cognitive disturbances: Aphasia (any impairment of the ability to use and/or understand words), Apraxia (difficulty in performing a learned movement or coordinated motor activity), Agnosia (loss of ability to recognize objects, people, sounds, shapes, or smells) or a disturbance in executive functioning such as abstract thinking, judgement and problem solving accompanied by functional impairment (inability to perform independently in activities of daily living) [15].

POTENTIAL FACTORS ON COGNITIVE IMPAIRMENT IN TYPE 2 DIABETES

Normally, type 2 diabetes does not exist in isolation. Other important factors that can affect cognition could take place in older diabetic patients leading to cognitive impairment [16]. Some factors that are likely to confound in the study of diabetes-related cognitive impairment are briefly discussed below.

Age

Cognitive impairment is often seen with the increasing age [8]. Ageing is also associated with changes in the brain. This change can be clearly seen in patients with Alzheimer's disease (AD) which show a decrease of glucose utilisation and deficient energy metabolism occur in the early stage of the disease. This suggests a role for impaired insulin signalling pathogenesis of AD [17]. Thus, the insulin receptor impaired in the brain due to ageing is also one of the causes of cognitive impairment.

Duration of diabetes

Longer duration of diabetes is associated with increased cognitive impairment [18]. In particular, longer duration of poor glycaemic control may lead to permanent cognitive impairment [19]. Duration of diabetes may cause the development of vascular disease when combined with high blood glucose in the body [20].

Obesity

Obesity or high body mass index (BMI) is associated with worse cognition [21], particularly in cognitive flexibility and memory. BMI was included as a covariate in blood pressure and blood cholesterol level in Gustafson et al.'s study [22]. There are many possibilities that BMI may link to cognitive decline in type 2 diabetes. A high BMI may lead to high blood pressure, and thus increase the risk of dementia [23]. High blood cholesterol may also cause a vascular risk factor and play a role in the etiology of AD [24].

Diabetic complications

A diabetes complication in microvascular lead to renal failure, foot ulcer and vision loss [25]. There is growing evidence that diabetes is associated with an increased risk of cognitive decline, physical disability and other conditions associated with geriatric syndrome [26]. These complications have an impact on the quality of life, loss of independence and may be of greater direct concern in older people with diabetes [27]. Diabetic complications may lead to chronic hyperglycaemia or long-term blood glucose and may also influence cerebral blood flow and neurotransmitter function, or nutrients to the brain [28].

Diabetic treatment

Lack of diabetic pharmacological treatment seems to be associated with a worse performance of cognitive function in older people with type 2 diabetes [18]. The study of Grodstein et al. [18] suggests that women who receive treatment (oral medication) perform better on the cognitive measures than the diabetic women who were reported to receive no medication. Diabetes medications can help control type 2 diabetes by increasing insulin sensitivity and decreasing glucose output. Consistent use of diabetes medications also helps to control blood glucose level and keep oxygen and nutrient reach brain cells [29].

Advanced glycation end products (AGEs)

Advanced glycation end products (AGEs) are a heterogeneous group of modified proteins, lipids, and nucleic acids implicated in the aging process and diabetes [30]. The modifications of proteins or lipids are the result of a chain of chemical reactions which follow an initial glycation reaction. Initial glycation involves covalent reactions between free amino groups of amino acids, such as lysine, arginine, and sugars (e.g. glucose, fructose and ribose), to create the Schiff base and then Amadori products, of which the best known are fructosamine (FAM) and

glycated haemoglobin (HbA1c) [31].

A high level of blood glucose (hyperglycaemia) is known to enhance the forming of early FAM and HbA1c, intermediate and advanced glycation products. These glycation products are a primary factor that initiates and promotes diabetic complications [32]. FAM fraction reacts much more quickly than the HbA1c to a change in glucose situation and reflects a quality of diabetes control over the short period of 2-3 weeks, while the degree of glycation of haemoglobin provides information about the glucose level over the last 6-8 weeks [33, 34]. It has long been recognized that increased HbA1c (a precursor of AGEs) levels are associated with a higher incidence of vascular complications in diabetic patients [30]. Hence, hyperglycaemia or increased HA1c (a precursor of AGEs) will induce the formation of AGEs, which acts as an important pathophysiological mechanism in the development of diabetic complications through binding and interaction with their receptors (RAGE). RAGE is expressed in many tissues such as heart, lung, skeletal muscle, and vessel wall [35]. The binding and interaction could then lead to an oxidative stress and activation of inflammatory pathways causing proatherosclerotic changes and inducing vessel damage [36]. More importantly, hyperglycaemia (increased HbA1c) could cause cognitive impairment by several mechanisms. Acute changes in blood glucose are known to alter regional cerebral blood flow and could also cause osmotic changes in cerebral neurons. These same mechanisms may be operative in the brain and induce the changes in cognitive function that have been detected in diabetic patients [37]. Moreover, AGEs are protein modifications that contribute to the formation of the histopathological and biochemical hallmarks of Alzheimer's disease (AD), i.e. amyloid plaques, neurofibrillary tangles and activated microglia in a brain [38]. AGEs may involve cognitive decline in type 2 diabetic patients from the glycation processes through hyperglycaemia or an increased HbA1c (precursor of AGEs) [30].

Glycaemic control

Glycaemic control is associated with cognitive function in type 2 diabetes. In particular, chronic glucose level appears to be associated with cognitive impairment in type 2 diabetes [29, 39, 40].

The level of glycaemic control (HbA1c) shows the association between the two cognitive domains (memory and executive function). HbA1c is defined in the two levels of controlled (HbA1c $\leq$ 7 or 53 mmol/mol) and inadequately controlled (HbA1c > 7 or 53 mmol/mol) [39, 41]. Memory impairment and executive dysfunction are associated with inadequately controlled diabetes in old adults with type 2 diabetes [39]. Uncontrolled glycaemia can lead to hyperglycaemia and cause slowly progressive pathogenesis of brain abnormalities that may eventually induce Alzheimer's disease (AD). Therefore, chronic hyperglycaemia could be one of the determinants of cognitive changes in people with diabetes [42].

Cardiovascular problems

Type 2 diabetes is a risk factor for vascular diseases such as hypertension. An interaction between type 2 diabetes and hypertension on cognitive performance is associated with a greater risk of poor performance on a test of memory and attention [43]. Hypertension may cause changes in vessel walls leading to ischemia or hypoxia of the brain, all of which are related to the development of AD pathology [44].

Inflammation

Inflammation may also contribute to cognitive impairment associated with type 2 diabetes. There is a link between inflammation and diabetes. For example, hyperglycaemia is associated with an increase in pro-inflammatory cytokines and other peripheral markers of inflammation [45]. Inflammation is also associated with an impaired glucose regulation and predicts the development of diabetes [46]. A high level of the inflammatory marker of C-reactive protein (CRP) and interleukin-6 (IL-6) is not only associated with an increased risk of developing type 2 diabetes [47] but also accelerated cognitive decline in healthy older adults [48] and in older adults with metabolic syndrome [49]. Moreover, decreasing brain levels of pro-inflammatory cytokines can reverse memory deficits [50, 51].

Depression

Another problem which may relate to cognitive impairment and affect self-care diabetes is depressive mood. Depression is a common co-morbidity of type 2 diabetes [52, 53]. People with diabetes are likely to suffer twice as often from depression as those without diabetes. Depressive symptoms may hinder diabetic patients' ability to adhere to diet, physical activity and oral medication [54-56]. Moreover, depression by itself is the most common of the reversible causes of cognitive impairment or pseudo-dementia, particularly in memory part [57]. Depression may also be associated with hippocampal atrophy caused by

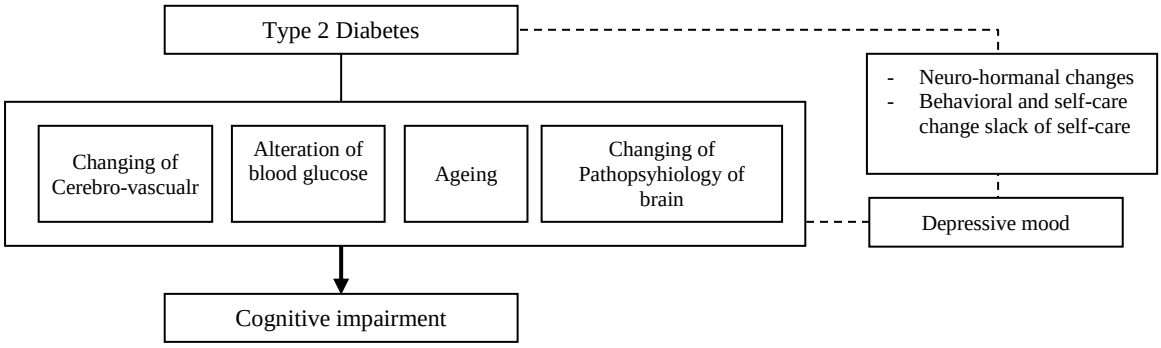

Figure 1 Proposed scheme, association of type 2 diabetes with cognitive impairment through changes in pathophysiology

elevated glucocorticiod secretions, resulting in memory impairment and dementia in later life [19]. In addition, depressive mood affects the HPA disturbances and causes prolonged hypercortisolemia. As a result, it may promote hippocampal atrophy and functional decline. This also affects impairment in the memory functions of the brain served by the hippocampus [58]. Moreover, depression might also play an important role in the maintenance of optimal glycaemic control in supporting the treatment adherence. Behavioural factors with depressive symptoms (lack of exercise and poor diet) also increase the risk of type 2 diabetes. The mechanisms linking depressive mood and type 2 diabetes may cause memory impairment.

In summary, the pathophysiological mechanisms suggest how diabetes-related factors can affect cognitive impairment through the brain. Vascular disease and alterations in glucose and amyloid metabolism seem to be important factors. In addition, the neuro-hormonal changes (activation of HPA) induced by depressive mood symptoms can lead to insulin resistance and develop of type 2 diabetes (Figure 1).

COGNITIVE FUNCTION AND DEPRESSIVE MOOD: IMPACT FOR DIABETES SELF-CARE

Cognitive impairment and depression have important consequences for diabetic patients and diabetes self-care management [59]. They are crucial components in the individual needs to control an appropriate blood glucose level (an optimal goal for diabetes care) by maximizing adherence to diet, exercise, and dosing schedules of the medicine [60]. It is important to recognize these two co-morbidities and great insight is needed in how cognitive impairment and depressive mood influence diabetes care and quality of life in diabetic patients [53]. Depressive symptoms may hinder their ability to adhere to diet, physical activity and oral hypoglycaemic agents [54-56], moreover, depression by itself is a reversible cognitive impairment, particularly in memory part [57].

Although diabetes is considered to be a risk factor for cognitive impairment [7, 43, 61], the cognitive function of patients with type 2 diabetes is not usually evaluated in routine clinical care. Cognitive impairment might be another factor associated with poor diabetes control and poor adherence of patients to educational approaches, such as diet orientations [62]. In addition, type 2 diabetes relies heavily on the principles of self-management. This is in essence a series of complex behaviours required for lifestyle and behavioural changes as well as adherence to medical interventions. Successful disease management is dependent on the patient's ability to execute these interventions and maintain lifelong adherence to diabetes care [63]. Hence, early detection and management of cognitive impairment and depressive mood may become an important aspect of diabetes care.

CONCLUSION

This paper reviews the possible factors related to cognitive impairment in type 2 diabetes and suggests that there are many factors related to cognitive impairment. In particular, depressive mood causes reversible cognitive impairment [57, 64, 65] and reduces capacity to manage a self-care regimen [66].

In Thailand, the prevalence of type 2 diabetes is about 7% and the highest prevalence (16.7%) is in the population aged 60 years and over [67]. Therefore, keeping good self-care management is an important factor in taking care of diabetes, a lifelong disease. In addition, the prevalence of diabetes and cognitive impairment increase with age, hence, screening cognition to identify early sign of cognitive impairment as well as screening depressive mood to detect a reversible cognitive

impairment in older diabetic patients would benefit an optimal diabetes care and planning.

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