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EDITORIAL

Total management of diabetes mellitus in the elderly

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The most recent Japanese demographic data confirm that the numbers of both children and adults are gradually and dramatically decreasing. In contrast, the number of older subjects is rapidly increasing, comprising more than 25 % of the total population in 2013. Thus, Japan is now the most aged society in the world. In addition, the 2012 Japanese national health and nutrition survey estimated that approximately 20.5 million subjects were either strongly suspected of having diabetes or had possible diabetes. In regard to age-specific incidence, about 40 % of males and 35 % of females over 60 years are suspected of having or likely to have diabetes. Several factors are proposed to account for this increasing incidence of diabetes and impaired glucose tolerance in the elderly. Sarcopenia, the decreased mass and function of skeletal muscles, is very important because it can induce insulin resistance [1]. Several mechanisms may be involved in the onset and progression of sarcopenia, which is classified as primary or age-related when no other causes are evident. The prevalence of primary sarcopenia in 65–70 year-olds ranges from 13 to 24 %, increasing to more than 50 % in those over 80 years [2]. Sarcopenia is associated with frailty, which is highly prevalent in old age, and confers a high risk for falls, disability, hospitalization and increased mortality [3]. A current systematic literature review has identified that cognitive impairment also has a serious effect on frailty [4].

In 2003, a Japanese survey reported that both the total number and ratio of patients with dementia are increasing year by year. However, a recent report has revised this data, with 2013 results classifying 4.5 million elderly Japanese subjects as having dementia, a greater than 15 % ratio among elderly persons in Japan. Diabetes mellitus is an established risk factor for dementia, with the frequency of vascular dementia increasing from 1.8-fold to 3.4-fold in subjects with diabetes mellitus compared to those without diabetes. On the other hand, the contribution of diabetes mellitus to the risk of developing Alzheimer's disease is less clear. However, a systematic review based on prospective studies indicates that almost all report risk ratios greater than one. In five well-conducted studies, this excess risk was statistically significant [5]. Thus, diabetes mellitus is likely to increase the risk of Alzheimer's disease by about twofold.

However, the role of diabetic complications as possible mechanisms in the development of dementia has not been well studied. Although acute hypoglycemia may be associated with cognitive impairment in children with type 1 diabetes, no studies have evaluated whether hypoglycemia is a risk factor for dementia in older patients with type 2 diabetes. A longitudinal cohort study followed up for 27 years indicated that a history of severe hypoglycemic episodes was associated with a greater risk of dementia [6]. On the other hand, a famous Japanese cohort study, the Hisayama study, also suggests that diabetes is a significant risk factor for all-cause dementia. Moreover, 2-h postload glucose levels, but not fasting plasma glucose levels, are closely associated with an increased risk of Alzheimer's disease [7].

Thus, both severe hypoglycemia and postprandial hyperglycemia are associated with cognitive decline, especially Alzheimer's disease. Rizzo et al. [8] reported that the increase in mean amplitude of glycemic excursions (MAGE) was significantly correlated with a decrease in mini mental status examination (MMSE). Since MAGE is a significant determinant of overall metabolic control, these

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studies strongly suggest that daily acute glucose swings are highly associated with cognitive decline in diabetes mellitus.

Gispen and Biessels [9] summarized the pathogenesis of diabetic encephalopathy in 2000. The pathogenesis can be divided into five main components: First, direct neurotoxic effects of hyperglycemia, including increased polyol pathway flux, oxidative stress and protein glycation; second, vascular changes, including alterations in cerebral blood flow and angiopathy; third, neurotropic changes including insulin and insulin-degrading enzyme (IDE); fourth, hypoglycemia; and fifth, the beta-amyloid cascade, are heavily associated with the pathogenesis of Alzheimer's disease. Recently, attention has focused on the direct association between insulin and IDE via the beta-amyloid cascade.

A mechanism attracting attention has been reported by Craft, stating that hyperinsulinemia caused by insulin resistance appears to be associated with the pathology of Alzheimer's disease [10]. Peripheral hyperinsulinemia induces a down-regulation of the transfer of insulin via the blood brain barrier, resulting in decreased insulin levels in the brain. Because insulin receptors are highly concentrated in the hippocampus, brain insulin signaling is particularly important for learning and memory. Furthermore, insulin promotes the release of intracellular beta-amyloid, and IDE seems to degrade beta-amyloid as well as insulin [11]. Lower levels of brain insulin inhibit the release of intracellular beta-amyloid. IDE is then not able to efficiently degrade beta-amyloid under these conditions of peripheral hyperinsulinemia, due to the competitive inhibition in enzyme–substrate interactions.

There are many ongoing clinical therapeutic strategies being investigated for Alzheimer's disease. One of these includes the insulin-sensitizing PPAR-gamma agonist, rosiglitazone, which improves insulin resistance [12]. Subjects with mild AD receiving rosiglitazone exhibited better delayed recall and selective attention. At 6 months, plasma beta-amyloid levels were unchanged from baseline in the treated-group, but declined in the placebo group, consistent with a recent report that plasma beta-amyloid decreases with progression of AD. Furthermore, intranasal insulin, which raises insulin acutely in the central nervous system without raising plasma insulin levels, has been shown to result in accumulation of insulin in the brain. Cognition was tested 15 min post-treatment, and insulin treatment facilitated recall on two measures of verbal memory in memory-impaired older adults [13].

The recent hypothetical model of dynamic biomarkers involved in the Alzheimer's pathological cascade has indicated that memory disturbance and changes of brain structures were already present before dementia or its preclinical stage, mild cognitive impairment (MCI), were clinically diagnosed. Furthermore, Tau-mediated neuronal injury and beta-amyloid deposition were almost completed [14]. About 50 % of the over 80 drugs being developed for Alzheimer's disease are aimed at effecting the beta-amyloid pathway, either by decreasing beta-amyloid production and aggregation, or by increasing beta-amyloid clearance. Another 25 % try to inhibit abnormal tau-phosphorylation. Among these developmental drugs, the PPAR-gamma agonists, rosiglitazone and pioglitazone are now being investigated in phase 3 and 2 trials, respectively. Another phase 2 study is evaluating intranasal nerve growth factor administration [15].

Biessels et al. [16] recently proposed pathophysiological mechanisms linking diabetes to changes in the brain and dementia. Diabetes and its comorbid conditions are associated with an increased risk of atherosclerosis and stroke, leading to vascular dementia. Glucose-mediated toxicity can lead to microvascular abnormalities and more widespread changes in cognition, referred to as accelerated brain aging. Additionally, diabetes and its treatment might interfere with amyloid metabolism, giving rise to Alzheimer's type pathology. Thus, diabetic dementia may be composed of these three etiologies, or even more.

In order to optimize management in the seriously increasing diabetic elderly, a large scale, randomized controlled intervention trial of Japanese elderly diabetes subjects (J-EDIT) was undertaken. This trial followed subjects for 6 years and examined the effects of multifactorial interventions on microvascular and macrovascular complications, mortality and prognosis of physical and cognitive functions. The clinical course of several parameters was compared between the conventional and intensive-treatment groups. A small, but significant difference in HbA1c between the two groups was observed 1 year after the start of intervention, although this significant difference was not observed after the second year. Significant differences in the other parameters, including BMI, total cholesterol, triglyceride (TG) and high-density lipoprotein (HDL) and non-HDL cholesterol, systolic and diastolic blood pressure, were not observed between the two groups during the follow-up period [17]. It is difficult to significantly reduce HbA1c, lipid levels, and blood pressure in the intensive-treated group, since a high prevalence of depression and hypoglycemic symptoms at baseline was notable. In addition, elderly patients do not accept an increase in the number of oral drugs or the initiation of insulin therapy.

However, a combination of these two groups was carried out to perform a landmark analysis 1 year after study entry, to evaluate the effects of glucose and lipid control. The patients were divided into quartiles of possible risk factors, and survival curves were compared; for example, the relation of HbA1c and incidence of stroke or all events related

to diabetes. The highest HbA1c quartile had an increased incidence of stroke and all diabetic events. However, the incidence of both events was not the lowest in the lowest quartile, suggesting the existence of a J-curve incidence according to HbA1c distribution. The same J-curve phenomena are shown in vascular events according to LDL-c distribution, and also in systolic blood pressure and incidence of stroke or all events related to diabetes [17].

This J-EDIT study provides significant information for improving the management of the diabetic elderly. The study chairman, Hideki Ito, of Tokyo Metropolitan Geriatric Hospital, concluded that not only control of blood glucose, but also comprehensive care, including blood pressure, dyslipidemia, and lifestyle, are important for the treatment of the elderly patients with diabetes mellitus [18].

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