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Effect of different blood glucose intervention plans on elderly people with type 2 diabetes mellitus combined with dementia

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Abstract. – OBJECTIVE: We analyzed the effects of intensive and mitigatory blood glucose control strategy on elderly people with type 2 diabetes mellitus (T2DM) combined with Alzheimer disease (AD).

PATIENTS AND METHODS: We enrolled 90 elderly patients with T2DM combined with AD to participate in this study. They were randomly divided into 3 groups: the control group, the strength group and the mitigation group with 30 cases in each group. In the control group, patients were only treated with diet and exercise while in the strength group patients were treated with oral hypoglycemic medications, subcutaneous insulin infusion or continuous infusion by micropump. Blood glucose level in the strength group patients was stabilized within 1 month (pre-meal ≤ 7.0 mmol/L, 2 hours post-meal glucose ≤ 12.0 mmol/L and glycosylated hemoglobin or HbA1c ≤ 7.0%). Personalized treatment programs were adopted for the mitigation group and the objective was to control the pre-meal blood glucose at ≤ 10.0 mmol/L (within 3 to 6 months) and also to control 2 hours post-meal blood glucose at ≤ 20.0 mmol/L (within 3 to 6 months). We compared the occurrence rate of diabetic complications, occurrence rate of new-onset dementia and progressive rate of dementia.

RESULTS: Our results showed that target glucose rate in the mitigation group was significantly higher than that in the strength group. The occurrence rate of diabetic complications in the mitigation group was significantly lower than that observed in the other two groups. Occurrence rate of diabetic hyperosmolar coma was significantly higher in the control group, the occurrence rate of hypoglycemia was meaningfully lower in the strength group and the occurrence rate of new-onset target-organ injury was considerably higher in the mitigation group. The occurrence rate of new-onset dementia and progressive rate of dementia in mitigation group was significantly lower than those in other two groups. Comparison between the control group and the strength group did not reveal any statistical significance ($p > 0.05$). In the meantime, the survival time in mitigation group was significantly longer.

CONCLUSIONS: Elderly patients with T2DM combined with AD may benefit more from the moderate control of blood glucose and a proper increase of the target value.

Key Words:
Blood glucose control, T2DM, AD, Complications, Survival rate.

Introduction

In China, the incidence rate of type 2 diabetes mellitus (T2DM) is high. The rate of T2DM control is low and the occurrence rate of T2DM complications is high, which seriously reduces the life quality and poses great pressure on families and the society[1-3]. Alzheimer disease (AD) is the main type of senile dementia, which seriously reduces the patients' cognitive ability and their self-help ability[4-6]. Results obtained from a prior study[7] showed that T2DM was an important independent risk factor that led to the occurrence of AD. It was also shown that the occurrence rate of AD for the patients whose blood glucose was poorly controlled could reach 10% to 30% within 10 years, which is the 25 to 35 times more than the rate observed in general population. Insulin and insulin-like growth factor (IGF) can mediate a variety of cell signal pathways including phosphatidylinositol 3-kinase (PI3K)/Akt and mitogen

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activated protein kinases/extracellular signal-regulated kinase 1/2 (MAPK/Erk1/2). Through this mediation they can have an impact on the sedimentation of the β-islet amyloid polypeptide (Aβ) and microtubule-associated protein (Tau) phosphorylation. They are also influential on the expression level of apolipoprotein E4, prion protein (PrP) and house-keeping gene (PRNP)[8] as well as the formation of tangles of nerves inside the neuron and extracellular amyloid plaques which is the most significant neuropathology tissue characteristics of AD. Due to the fact that blood vessel injury mechanism in T2DM involves the endothelial dysfunction, oxidative stress and immune disorder, T2DM also plays an important role in vascular dementia[9]. Therefore, the scientific and proper control of blood glucose, as well as the stabilization of blood glucose level, can play an extremely important role in reducing the occurrence rate of T2DM complications. The objective of controlling blood glucose is specified in several handbooks in various countries and it is recommended for physicians to adopt different blood glucose target range for different people in order to reduce the occurrence rate of complications and achieve the greatest effect under the premise that the blood glucose is controlled[10-12].

There are only few studies focused on elderly T2DM combined with AD. Controlling the blood glucose level in AD patients is relatively harder, and the objective of blood glucose control is to see how many patients can benefit from the specified treatment plan to the largest extent and whether the intensive or mitigatory blood glucose control plan is both safe and effective. The clinical observation and follow-up visits adopted by our center yielded a great deal of samples and produced concrete results that are discussed here.

Patients and Methods

Patients

From January 2012 to June 2013, a total of 90 elderly patients who were diagnosed with T2DM combined with AD were enrolled for this study. We used the WHO standards to diagnose AD (forth edition of *Diagnostic and Statistical Manual of Mental Disorders* aka DMS-IV, issued by American Psychiatric Association).

Cases with following criteria were excluded: (1) patients with secondary dementia including brain surgery, trauma history, tumor history; (2) patients with non-AD type dementia such as vascular dementia, severe dementia, complete loss of cognitive ability and self-help ability; (3) patients who failed to complete blood glucose control and monitoring, guardians' incoordination; (4) patients who failed to complete the blood glucose administration work in accordance with corresponding requirements, or failed to acquire complete clinical data or quit the study in the midway and or those who participated in other researches.

This research was approved by the Ethics Committee of our hospital and the informed consent was obtained from patients and their guardians. Using random number table patients were divided into 3 groups: the control group, the strength group and the mitigation group with 30 cases in each group. In the control group, there were 20 males and 10 females with ages ranging from 53 to 77 years (average = 65.4 ± 8.2). The duration of dementia was 1 month to 1 year (average = 5.6 ± 2.3 months). The pre-meal glucose for the control group was 7.5 to 26.8 mmol/L (average = 7.9 ± 4.5 mmol/L) and the 2 hours post-meal blood glucose was 14.6 to 36.6 mmol/L (average = 19.8 ± 5.6 mmol/L). The glycosylated hemoglobin HbA1c was 7.3 to 14.5% (average = 11.2 ± 3.3%). In the control we had 10 patients with diabetes mellitus combined with hypertension, 6 patients with stroke and 4 patients with coronary heart disease. In the strength group, there were 19 males and 11 females with ages ranging from 54 to 79 years (average = 65.5 ± 8.3 years). The duration of dementia ranged from 1.5 months to 2 years (average = 5.8 ± 2.2 months). Pre-meal blood glucose in the strength group ranged from 7.6 to 27.3 mmol/L (average = 18.0 ± 4.7 mmol/L) and the 2 hours post-meal glucose was 15.0 to 37.2 mmol/L (average = 21.2 ± 5.8 mmol/L). HbA1c in the strength group was 7.0 to 14.3 % (average = 11.0 ± 3.2%). In the strength group, there were 9 patients with diabetes mellitus combined with hypertension, 5 patients with stroke and 5 with coronary heart disease. In the mitigation group, there were 18 males and 12 females and their ages ranged from 56 to 80 years (average = 65.7 ± 8.5 years) and duration of dementia was from 1.5 months to 2.5 years (average = 5.9 ± 2.3 months). The pre-meal blood glucose ranged from 7.7 to 27.0 mmol/L (average = 18.1 ± 4.5 mmol/L) and the 2 hours post-meal glucose ranged from 15.2 to 37.4 mmol/L (average = 21.3 ± 5.6 mmol/L). HbA1c in the mitigation group was 7.1 to 14.5% (average = 11.2 ± 3.4%). There are 11 patients with diabetes mellitus combined with hypertension, 3 patients with stroke and 3 with coronary heart disease

in the mitigation group. Comparison of baseline data among three groups did not demonstrate any statistically significant difference ($p > 0.05$).

Research Method

The blood glucose of patients was not intervened in the control group and patients were only treated with diet and exercise. In the strength group, patients were treated with oral hypoglycemic medications, subcutaneous insulin infusion or continuous infusion by micropump. This way, strength group's patients blood glucose level was stabilized within 1 month (pre-meal ≤ 7.0 mmol/L, 2 hours post-meal glucose ≤ 12.0 mmol/L, glycosylated hemoglobin HbA1c ≤ 7.0%). Personalized treatment programs were adopted for patients in the mitigation group. The objective for the blood glucose was as follows: pre-meal blood glucose ≤ 10.0 mmol/L within 3 to 6 months and 2 hours p ost-meal blood glucose ≤ 20.0 mmol/L within 3 to 6 months.

Observation Target

Comparative studies were on target glucose rate, the occurrence rate of diabetic complications, the occurrence rate of new-onset dementia; the progressive rate of dementia and survival time were made. The diabetic complications including hypoglycemia, diabetic hyperosmolar coma, new-onset target organ injury (such as fundal hemorrhage, diabetic nephropathy, adverse cardiac and cerebral events and peripheral vascular injury) and Folstein mini-mental state examination (MMSE) were adopted to test intelligent status. AD examination scale (ADASC-Cog) was used to test cognitive function, Wechsler-modified memory scale was employed to test memory, the activity of daily living scale was adopted to test activity of daily living, Hamilton depression scale was used to test depressive state, the modified Hachinski ischemia rating scale was adopted to identify vascular dementia and the clinical dementia rating (CDR) was used to assess the severity of dementia. Also, patients' neurological function was comprehensively assessed and those patients with aggregated disease were confirmed to have the tendency of dementia as the score increased. The follow-up visits were conducted until January 2016 and the average time for follow-up visits was about 3 years.

Statistical Analysis

SPSS19.0 statistical software (SPSS Inc., Chicago, IL, USA) was to conduct data analyses. Quantitative data were expressed by the mean±-standard deviation and the comparison among groups was done using single factor ANOVA. Qualitative data were reported by number of cases or percentage (%), while the comparison among groups was tested by X^2. Survival time was tested by Kaplan-Meier method or Log-rank. $p < 0.05$ showed that the difference had statistical significance.

Results

Comparison of Glucose Target Rate of Diabetes and Occurrence Rate of Diabetic Complications

The target glucose rate of patients in the mitigation group was significantly higher than that of patients in the strength group while the occurrence rate of diabetic complications in the mitigation group was significantly lower than that in other two groups. Differences were statistically significant ($p < 0.05$). The occurrence rate of diabetic hyperosmolar coma was higher in the control group and the occurrence rate of hypoglycemia was higher in strength group while the occurrence rate of new-onset target organ injury was higher in the mitigation group. Comparison between the control group and the strength group revealed no statistically significant differences ($p > 0.05$) (Table I).

Table I. Comparison between glucose target rate of diabetes and occurrence rate of diabetes related complications.

Groups	Number of cases	Target rate	Hypoglycemia	Diabetic hyperosmolar coma	New-onset target organ injury	Occurrence rate of total complications
Control group	30	–	1 (3.3)	10 (33.3)	4 (13.3)	15 (50.0)
Strength group	30	16 (53.3)	8 (26.7)	4 (13.3)	2 (6.7)	14 (46.7)
Mitigation group	30	24 (80.0)	1 (3.2)	2 (6.7)	3 (10.0)	6 (20.0)
χ^2		4.800		11.554		6.826
p		0.028		0.021		0.033

Table II. Comparison of occurrence rate of new-onset dementia and progressive rate of dementia.

Groups	Number of cases	New-onset dementia	Progressive rate of dementia
Control group	30	11 (36.7)	10 (33.3)
Strength group	30	9 (30.0)	8 (26.7)
Mitigation group	30	3 (10.0)	2 (6.7)
χ^2		6.074	6.686
p		0.048	0.035

Comparison of Occurrence Rate of New-Onset Dementia and Progressive Rate of Dementia

The occurrence rate of new-onset dementia in the mitigation group was considerably lower than that in the other two groups. The difference was statistically significant ($p < 0.05$). The difference between the control group and the strength group had no statistical significance ($p > 0.05$) (Table II).

Comparison of Survival Time

The survival rate in the mitigation group was significantly higher and the difference had statistical significance ($\chi^2 = 32.308$, $p < 0.001$) (Figure 1).

Discussion

Currently, there is no effective therapy method for elderly dementia cases. Dementia tends to be aggregated progressively and fatality rate of this disease may reach 20% to 38% in 5 years[13,14]. There are about 1.5 million patients diagnosed with diabetes-related dementia, to whom a practical and effective management plan is vital. Patients with mild dementia tend to delay the disease course and improve their life quality under the assistance of family members, social activities, health care system, standardized pharmaceutical intervention and regular follow-ups[15]. Some specialists believe[16] that patients would benefit more from intensive pharmaceutical interventions. In the hospital, patients can control their blood glucose in a short term by several methods: (1) taking hypoglycemic drugs; (2) taking medium-acting or shot-acting subcutaneous insulin infusion; (3) using pre-meal or post-meal blood glucose regulation by combined short-acting insulin and use of micro-insulin pump for 1 to 3 months[17-19]. Results obtained during clinical observation and

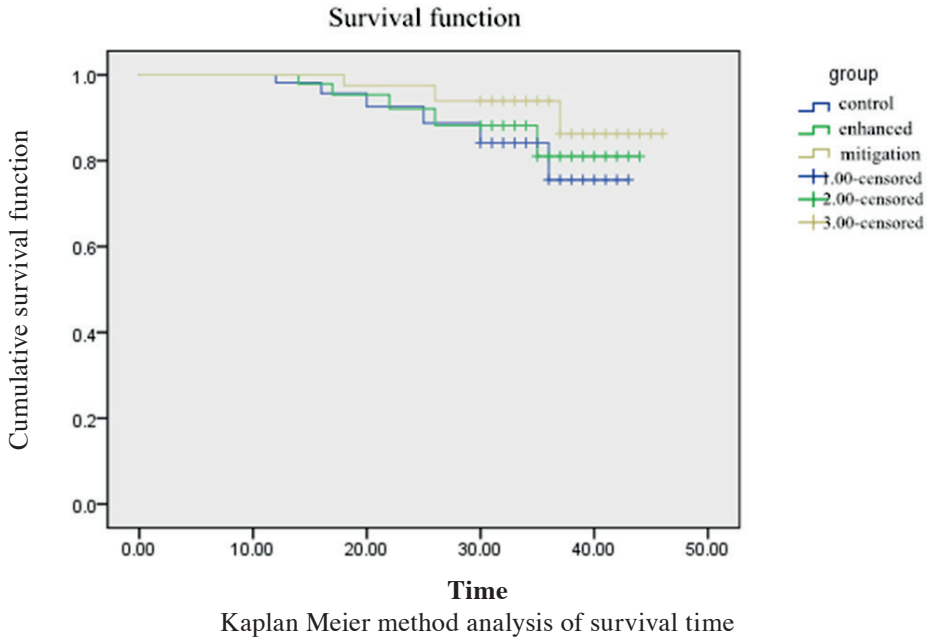

Figure 1. Kaplan Meier analysis on survival time.

follow-up visits showed that there were many influential factors affecting the success rate of blood glucose control including the physicians' attention, patients' cooperation, frequency of follow-ups and the impact of other diseases, Final target rate was only 10% to 30% and the occurrence rate of secondary blood glucose disorders (for patients who suffered from the disease for 6 to 12 months) was 50% to 65%, which could lead to treatment failure. It was shown that the target glucose rate in the strength group reached 53.3%, (which was the higher level) and the occurrence rate of complications was 46.7%. The occurrence rate of hypoglycemia was 26.7% which showed that the intensive blood glucose control was not suitable for the elderly patients with T2DM and AD because it was more difficult to apply blood glucose control to AD patients (poor execution). Failure to control the blood glucose could easily occur in AD patients due to an increase in insulin resistance[20,21].

We planned a 3-year of follow-up visits to the elderly patients with T2DM combined with AD. Results obtained from comparison made among the three control strategies including non-intervention, intensive blood glucose control and moderate blood glucose control revealed that: (1) the glucose target rate in mitigation group was significantly higher than that in the strength group and (2) the occurrence rate of diabetic complications in mitigation group was significantly lower than that in the two other groups. The occurrence rate of diabetic hyperosmolar coma was higher in the control group and the occurrence rate of hypoglycemia was lower in the strength group, while the occurrence rate of new-onset target organ injury was higher in the mitigation group. The personalized treatment plan is recommended by the moderate blood glucose control strategy. This strategy emphasizes on the control of blood glucose according to the actual conditions of patients, including the patients themselves and their families. This strategy recommends the physicians' intervention only in the cases of higher and wider fluctuation range. By using this strategy, patient can significantly reduce the occurrence rate of diabetic hyperosmolar coma and hypoglycemia. As we showed, the occurrence rate of new-onset dementia and progressive rate of dementia in the mitigation group were significantly reduced compared to the other two groups. Also, the survival time in mitigation group increased considerably. It was shown that the moderate blood glucose control played an important role in delaying the process of dementia and prolonging the long-term survival time.

Conclusions

The elderly patients with T2DM combined with AD may benefit more from moderate blood glucose control and an appropriate increase of target value.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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