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Original Article

Effect of a relaxed glycemic control goal on elderly type 2 diabetic nephropathy

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Abstract: Objective: The goal of this study was to investigate the effect of a relaxed glycemic control goal, namely HbA1c < 8.0%, on type 2 diabetic nephropathy in elderly patients. Methods: A total of 196 elderly patients with type 2 diabetic nephropathy were included. Body mass index (BMI), blood pressure, fasting blood glucose, postprandial 2-hour blood glucose, blood lipids, blood urea nitrogen, serum creatinine, HbA1c, urinary microalbumin/urine creatinine (ACR), and estimate glomerular filtration rate (eGFR) were measured. Results: Two patients were excluded from the study due to increased blood pressure and left lower lobe pneumonia. According to the level of HbA1c, patients were divided into group I (HbA1c < 8%) and II (HbA1c ≥ 8%). There were no significant differences in basic characteristics such as age, gender, or BMI between two groups ($P > 0.05$). However, insulin therapy was significantly increased in group II compared with that in group I ($P < 0.01$). Fasting blood glucose, postprandial blood glucose, and HbA1c were significantly lower in group I than that in group II ($P < 0.01$). Although blood urea nitrogen, serum creatinine, and eGFR exhibited no statistical difference between the two groups ($P > 0.05$), urinary microalbumin and ACR in group I patients were significantly lower than those in group II [Albumin: ($P < 0.05$), ACR: ($P<0.05$)]. Furthermore, the incidence of diabetic nephropathy was also reduced. Conclusion: Relaxed glycemic control goal (HbA1c < 8.0%) reduces urinary albumin excretion, the incidence of diabetic nephropathy, and long-term end-stage renal disease without increasing the risk of hypoglycemia in elderly diabetic patients.

Keywords: Diabetes, glycosylated hemoglobin, microalbumin

Introduction

Epidemiological surveys show that the prevalence of diabetes in China reaches 9.7% [1]. Previous studies confirmed that intensive blood glucose control as HbA1c < 6.0-7.0% can reduce 25% of diabetic microangiopathy, 33% of microalbuminuria, and 60% of retinal, renal, nervous system complications, but increases the incidence of hypoglycemia [2-5]. The type 2 diabetes (T2DM) blood glucose control target which is recommended by the 2013 Chinese Guidelines for the Prevention and Treatment of T2DM is HbA1c < 7.0% [6]. It also proposes a relaxed blood glucose control target as HbA1c < 8.0%, which is more suitable for some special patient groups.

The common characteristics of elderly patients with diabetes are long duration of illness, poor blood glucose control, multiple complications and comorbidities, poor tolerance to hypoglycemia, and limited survival [7-9]. There is still controversy surrounding blood glucose control goal for these patients. In addition, more and more evidence has revealed that HbA1c is a gold standard reflecting long-term blood glucose changes in patients with diabetes, which can also predict the risk of complications [10-12]. Therefore, T2DM patients aged over 65 years old were retrospectively selected to investigate whether the relaxed blood glucose control goal (HbA1c < 8.0%) is more safe and beneficial for these patients.

Materials and methods

Research subjects

A total of 196 elderly T2DM patients aged ≥ 65 years (140 males and 56 females) with a mean age of 79.98±7.30 years during Jan 2016 and Dec 2017 in our hospital were included. The diagnosis of all patients met the WHO Diagnostic Criteria for T2DM in 1999 [13]. Inclusion crite-

ria: no hypoglycemia during hospitalization, body mass index (BMI) < 24 kg/m^2, blood pressure < 140/80 mmHg, low-density lipoprotein cholesterol (LDL-C) < 2.6 mmol/L. Exclusion criteria: type 1 diabetes and secondary diabetes, T2DM with acute complications, patient with urinary tract infection, severe liver and kidney disease, advanced cancer, anemia, and splenomegaly, and non-diabetic nephropathy patients. This study was pre-approved by the Ethical Committee of Shanghai Fourth People's Hospital, Affiliated to Tongji University School of Medicine. All subjects signed consent forms before recruitment in this study.

Methods

Height, weight, BMI, and blood pressure were measured. The comorbidity disease examination and diagnosis were performed according to the "Standards of care for type 2 diabetes in China" [6]. The diagnostic standard of hypoglycemia is fasting or random blood glucose ≤ 3.9 mmol/L with or without symptoms. Fasting blood glucose (hexokinase·G-6-PDH method), urea nitrogen (GIDH method), creatinine (HMMPS method), HbA1c (high performance liquid chromatography), total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-C), and high High-density lipoprotein cholesterol (HDL-C) were measured. Insulin was subcutaneously injected at 15-30 minutes before meals. After diabetic breakfast, postprandial 2-hour blood glucose (hexokinase G-6-PDH method) was measured after 2 hours. Urinary albumin/urine creatinine (ACR) test (immunoturbidimetry) was performed for 3 times, and 2 times of elevation (male > 2.5 mg/mmol, female > 3.5 mg/mmol) was considered as diabetic nephropathy [14].

Estimated glomerular filtration rate (eGFR) was calculated from the Cockcroft-Gault (C-G) formula:

Male Ccr = (140-age) × body weight (kg) × 1.23/creatinine (μmol/L)

Female Ccr = (140-age) × body weight (kg) × 1.03/creatinine (μmol/L)

Statistical analysis

SPSS17.0 was used for statistical analysis. All data are expressed as mean ± standard deviation (SD), and the rate is presented as percentage. The data were compared by student t-test or Chi square test. $P < 0.05$ was considered as statistical significance.

Results

General information

One male patient with increased blood pressure up to 150/90 mmHg and Another male patient with left lower lobe pneumonia during hospitalization were excluded. A total of 194 patients were included in the study. According to HbA1c < 8% and HbA1c ≥ 8%, patients were divided into group I (92 cases) and II (102 cases). There were no significant differences in age, gender, BMI, duration of diabetes, hypertension, coronary heart disease, atherosclerosis of the lower extremities, sequelae of cerebral infarction between two groups ($P > 0.05$). However, insulin therapy was significantly increased in group II compared with group I (82.35% vs. 41.30%, $x^2 = 34.92$, $P < 0.01$). However, the usage of oral hypoglycemic drugs, ACEI/ARB, and CCB were similar between two groups ($P > 0.05$) (**Table 1**).

Blood glucose control and diabetic nephropathy

Fasting blood glucose, postprandial blood glucose, and HbA1c were significantly lower in group I than those in group II [fasting plasma glucose: (6.42±1.43) mmol/L vs. (9.20±2.29) mmol/L, $P < 0.01$; postprandial 2-hour blood glucose: (10.87±2.43) mmol/L vs. (15.42±3.13) mmol/L, $P < 0.01$; HbA1c: (6.83±0.45)% vs. (9.86±1.28)%, $P < 0.01$]. Although blood urea nitrogen, serum creatinine, and eGFR exhibited no statistical differences between the two groups ($P > 0.05$), urinary microalbumin and ACR in group I patients were significantly lower than those in group II [Albumin: (27.98±25.10) mg/L vs. (54.53±50.92) mg/L, $P < 0.05$; ACR: (5.25±4.16) mg/mmol vs. (11.85±10.01) mg/mmol, $P < 0.05$]. Additionally, the incidence of diabetic nephropathy was also reduced by 19.18% (54.35% vs. 73.53%, $P < 0.01$) (**Table 2**).

Discussion

An epidemiological survey in 2007-2008 reported that the prevalence of diabetes among the elderly over 60 was much higher than that of people aged 20-30 [1]. Moreover, with the

Table 1. General information

	Group I (HbA1c < 8%)	Group II (HbA1c ≥ 8%)	χ^2 or *t* value
Cases	92	102	
Male	68	70	0.66
Age (years old)	81.01±7.44	79.06±6.81	1.56
BMI (kg/m^2)	22.80±2.38	23.23±1.84	1.11
Diabetes duration (year)	13.54±4.90	14.26±8.28	1.13
Hypertension duration (year)	9.43±7.30	10.31±10.01	0.53
Systolic pressure (mmHg)	129.22±8.16	130.73±8.58	1.10
Diastolic pressure (mmHg)	72.83±6.29	74.61±6.84	1.59
Coronary heart disease (%)	45.65	41.18	0.39
Atherosclerosis of the lower extremities (%)	34.78	35.29	0.0056
Sequelae of cerebral infarction (%)	50.00	47.06	0.17
Drug therapy			
Insulin (%)	41.30	82.35**	34.92
Oral hypoglycemic drugs (%)	78.26	76.47	0.068
ACEI/ARB (%)	43.48	43.14	0.023
CCB (%)	36.96	43.14	0.77

***P* < 0.01.

Table 2. Blood glucose control and diabetic nephropathy

	Group I (HbA1c < 8%)	Group II (HbA1c ≥ 8%)	χ^2 or *t* value
HbA1c (%)	6.83±0.45	9.86±1.28**	17.82
Fasting blood glucose (mmol/L)	6.42±1.43	9.20±2.29**	7.94
Postprandial blood glucose (mmol/L)	10.87±2.43	15.42±3.13**	8.75
Blood urea nitrogen (mmol/L)	6.72±2.27	6.40±2.25	0.70
Creatinine (μmol/L)	87.63±25.51	79.31±27.70	1.52
eGFR (ml/min·1.73 m^2)	53.84±16.60	57.59±16.88	1.28
Urinary microalbumin (mg/L)	27.98±25.10	54.53±50.92*	2.13
ACR (mg/mmol)	5.25±4.16	11.85±10.01*	2.41
Diabetic nephropathy (%)	54.35	73.53**	7.77

**P* < 0.05; ***P* < 0.01.

improvement of the control level of various risk factors for diabetic complications, the survival time of diabetic patients has increased. Diabetic patients suffer from a long duration of illness, poor glycemic control, multiple complications and comorbidities, poor tolerance for hypoglycemia, and limited survival [15], which is a big challenge for the clinical treatment with common diabetic patients.

The UK Prospective Diabetes Study (UKPDS) [2] suggested that intensive glucose control resulted in fasting blood glucose < 6 mmol/L and HbA1c < 7%, which can reduce 25% of diabetic microangiopathy and 33% of microalbuminuria. After a 7-year observation by the American Diabetes Control and Complications Trial (DCCT) [4], although intensive glycemic control did not reach the expected target of HbA1c < 7%, reducing HbA1c to 7.2% alone could also reduce overall diabetes-associated complications by 60%. However, the incidence of hypoglycemia in patients with intensive glycemic control was increased 3-fold compared with conventional treatment. This data raise concerns about hypoglycemia. In particular, ACCORD result suspected whether blood glucose control should be as low as possible, since intensive blood glucose control significantly enhance the risk of death [5].

According to the results of previous large-scale clinical trials, China formulated the "Standards of care for type 2 diabetes in China", recommending that T2DM control target was HbA1c < 7.0% [6]. Moreover, a relaxed control target HbA1c < 8.0% has been proposed to be more suitable for patients with long period of illness, significant microvascular or macrovascular complications, history of severe hypoglycemia, and a short life expectancy. Whether the relaxed goal (HbA1c < 8.0%) is more suitable for glycemic management in elderly diabetics has been controversial.

In this study, only 47% of elderly patients with diabetes over 65 years old did not experience hypoglycemia in hospital with blood pressure, and LDL-C, and BMI control achieved the re-

laxed goal (HbA1c < 8.0%). The remaining 53% of the patients exhibited significantly increased fasting and postprandial blood glucose levels with the average HbA1c up to 9.86%. Despite the usage of insulin plus oral hypoglycemic combination therapy, blood glucose is still difficult to control, indicating that the glycemic control in elderly diabetics is ineffective. There are several reasons. First of all, it may be related to the fact that elderly patients with diabetes are afraid of hypoglycemia, leading to poor dietary control. Second, long-term diabetic islet function depletion also makes blood glucose difficult to control. The lack of clear evidence-based medical basis for clinicians to manage patients to decrease blood glucose level is also a factor that cannot be ignored.

Long-term sustained hyperglycemia can lead to elevated urinary microalbumin excretion and increase the incidence of diabetic nephropathy and end-stage renal disease [16]. The mechanism of hyperglycemia's effect on the kidneys is not clear, which may be related to hyperglycemia, advanced glycation end products, increased metabolic bypass of polyols, increased hexosamine pathways, activation of the PKC pathway, as well as changes of hemodynamics [17]. In the present study, although only 47% of patients achieved relaxed blood glucose level (HbA1c < 8.0%) without significant changes in blood urea nitrogen, serum creatinine, and eGFR, they also exhibited reduced urinary ACR, and the incidence of diabetic nephropathy. Although this result is not as significant as ADVANCE in diabetic nephropathy [3], the ADVANCE study achieved the goal with the development of the risk of severe hypoglycemia. Due to a limited number of patients enrolled in the present study, a large prospective cohort clinical trial is required to confirm the findings in the future.

Conclusion

Relaxed glycemic control goal (HbA1c < 8.0%) reduces urinary albumin excretion, the incidence of diabetic nephropathy, and long-term end-stage renal disease without increasing the risk of hypoglycemia in elderly diabetic patients.

Disclosure of conflict of interest

None.

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