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Editorial Board Member of *World Journal of Diabetes*, Yan-Kai Xia, BMed, PhD, Professor, Vice President, Nanjing Medical University, Nanjing 211166, Jiangsu Province, China. yankaixia@nimu.edu.cn

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EDITORIAL

Individualized intensive insulin therapy of diabetes: Not only the goal, but also the time

Yun Hu, Hong-Jing Chen, Jian-Hua Ma

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Yun Hu, Hong-Jing Chen, Department of Endocrinology, The Affiliated Wuxi People's Hospital of Nanjing Medical University, Wuxi People's Hospital, Wuxi Medical Center, Nanjing Medical University, Wuxi 214023, Jiangsu Province, China

Jian-Hua Ma, Department of Endocrinology, Nanjing First Hospital, Nanjing 210000, Jiangsu Province, China

Corresponding author: Jian-Hua Ma, MD, Professor, Department of Endocrinology, Nanjing First Hospital, No. 32 Gongqingtuan Road, Nanjing 210000, Jiangsu Province, China.
majianhua@china.com

Abstract

Intensive insulin therapy has been extensively used to control blood glucose levels because of its ability to reduce the risk of chronic complications of diabetes. According to current guidelines, intensive glycemic control requires individualized glucose goals rather than as low as possible. During intensive therapy, rapid blood glucose reduction can aggravate microvascular and macrovascular complications, and prolonged overuse of insulin can lead to treatment-induced neuropathy and retinopathy, hypoglycemia, obesity, lipodystrophy, and insulin antibody syndrome. Therefore, we need to develop individualized hypoglycemic plans for patients with diabetes, including the time required for blood glucose normalization and the duration of intensive insulin therapy, which deserves further study.

Key Words: Diabetes; Intensive therapy; Insulin; Treatment-induced neuropathy

Core Tip: Intensive insulin therapy is popular in the treatment of patients with diabetes. This article highlighted the effects and side effects of intensive insulin therapy. It is a warning against the use of insulin therapy without any limitations, such as the speed of blood glucose lowering and the duration of insulin therapy.

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INTRODUCTION

Intensive insulin therapy refers to the control of blood glucose levels within the normal range using insulin therapy in patients with poor glycemic control. Intensive insulin therapy has been demonstrated to effectively decrease the risk of chronic complications in both patients with type 1 and type 2 diabetes[1,2]. The Diabetes Control and Complications Trial [3] in 1993 and the United Kingdom Prospective Diabetes Study[4] in 1998 are landmark studies that demonstrated the benefits of intensive insulin therapy in type 1 and type 2 diabetes, respectively. Moreover, intensive insulin therapy has favorable outcomes in the recovery and maintenance of β-cell function and protracted glycemic remission compared to treatment with oral hypoglycemic agents in patients newly diagnosed with type 2 diabetes[5]. Therefore, intensive insulin therapy is administered widely among patients with diabetes due to its benefits. Furthermore, the standards of insulin intensive therapy are constantly updated, and the side effects identifiedare summarized briefly in the present commentary.

INDIVIDUAL GOALS FOR INTENSIVE THERAPY

Most current diabetes guidelines recommend individualized goals for intensive glycemic control. The Action to Control Cardiovascular Risk in Diabetes study found that low glycemic control with a goal of HbA1c < 6.0% led to increased mortality in patients with type 2 diabetes[6]. As such, the goal of intensive therapy is not as low as possible, and the increased risk of hypoglycemia should be considered. According to the guidelines of the American Diabetes Association and the Chinese Diabetes Society, the reasonable HbA1c goal for most nonpregnant adults is < 7%, which is beneficial for reducing microvascular and macrovascular complications in type 1 and type 2 diabetes[7,8]. The East African Diabetes Study Group recommended a target HbA1c of 7.5% for all children with type 1 diabetes mellitus[9]. More stringent HbA1c targets (such as < 6.5%, or even close to the normal reference value) and less stringent HbA1c goals (such as < 8.0%) are indicated depending on the duration of disease, life expectancy, complications, risk of hypoglycemia, and other adverse effects of treatment[10,11].

SIDE EFFECTS OF RAPID BLOOD GLUCOSE REDUCTION

Clinicians and even patients usually recommend blood glucose recovery to the glycemic target as soon as possible during intensive therapy, usually within a week[5,12], and this is the same when patients initially use an automatic insulin delivery system[13,14]. During intensive therapy, HbA1c can be dramatically reduced by more than 1.5%-2% in 3-4 mo [15,16], and 3%-4% in a year[16,17]. Several studies have reported that rapid blood glucose reduction can aggravate various complications, including cardiovascular events[16], retinopathy[17], nephropathy[18] and neuropathy[15,19]. Neuropathy induced by an abrupt improvement in glycemic control is called treatment-induced neuropathy in diabetes (also referred to as insulin neuritis). All these complications commonly occur in patients with chronic hyperglycemia, the incidence rate and severity are positively correlated with the magnitude and speed of the decrease in HbA1c[15,16]. Therefore, the planning of a individualized intensive therapy program to prevent these complications requires further research. Hence, the duration of hyperglycemia, HbA1c levels, and preexisting complications at baseline should be considered.

OVERUSE OF INSULIN IN PATIENTS WITH TYPE 2 DIABETES

With the popularity of short-term intensive therapy, many patients with type 2 diabetes are prescribed insulin therapy at the time of the new diagnosis; However, some of these patients do not evaluate the possibility of insulin withdrawal in time[20]. Some patients had been using insulin for several years. Although these patients can maintain good glycemic control, the excessive and prolonged use of insulin can result in certain side effects. More treatment-induced neuropathy and retinopathy have been reported in patients receiving insulin therapy than in patients treated with oral hypoglycemic agents[21]. Not only because insulin reduces HbA1c the most[22] but because the abnormal activation of the insulin-IGF-1-AKT signaling pathway may exacerbate these complications[22,23]. In our previous study using flash glucose monitoring, about 40% of patients with type 2 diabetes using premixed insulin had time below range ≥ 4%, illustrating a high proportion of hypoglycemia; Meanwhile, the proportion of oral hypoglycemic agents treatments combination was less than 50%[24]. Moreover, the long-term use of insulin and hyperinsulinemia in patients with type 2 diabetes may lead to obesity[25] and insulin resistance, lipodystrophy[26,27], and exogenous insulin antibody syndrome[28]. These problems

lead to the deterioration of glycemic control. Therefore, when and under what circumstances intensive insulin therapy can be stopped and switched to oral hypoglycemic agents must be emphasized in patients newly diagnosed with type 2 diabetes.

CONCLUSION

To control the side effects of intensive insulin therapy, individualized glycemic goals and hypoglycemic plans need to be developed for patients, including the time required for blood glucose levels to reach the target and the duration of intensive insulin therapy. Oral glucose-lowering drugs and the GLP-1 receptor agonist adjunct to insulin can help reduce the insulin dose and improve glycemic variations[29,30], and should be initiated simultaneously with intensive insulin therapy in patients with type 2 diabetes and even in some patients with type 1 diabetes who have insulin resistance[31]. Furthermore, some nerve and microvascular protectors, such as epalrestat[32], mecobalamin[33], and pancreatic kininogenase[34], may helpprevent these complications of intensive therapy, which needs further clinical studies.

FOOTNOTES

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ORCID number: Jian-Hua Ma 0000-0001-9383-2559.

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