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JDI UPDATES

New perspectives on insulin therapy

Insulin was discovered by Banting and Best in 1921, and was subsequently applied for the treatment of diabetes. Porcine or bovine insulin purified from their pancreas had been used clinically for >50 years until the development of the methods to produce recombinant human insulin by genetic engineering techniques. The Diabetes Control and Complications Trial[1] and our Kumamoto Study[2] provided the evidence that better glycemic control could be obtained by intensive insulin therapy consisting of the supplementation of both basal and postprandial insulin, which in turn resulted in the prevention of the initiation and progression of diabetic microvascular complications.

For the intensive insulin therapy with multiple insulin injections of these studies, a combination of intermediate-acting neutral protamine Hagedorn insulin and short-acting (regular) insulin, which covers basal insulin secretion and postprandial insulin secretion, respectively, was used. Since the late 1990s, in order to achieve longer and flatter action than neutral protamine Hagedorn insulin, long-acting insulin analogs have been developed, and to achieve quicker onset and shorter duration of action than regular insulin, rapid-acting insulin analogs have been invented. Utilization of these insulin analogs could reduce the risk of hypoglycemia and achieve better glycemic control in patients with diabetes.

In addition to the improvement of insulin therapy using such insulin analogs, new oral anti-diabetic agents, including dipeptidyl peptidase-4 inhibitors and sodium–glucose cotransporter 2 inhibitors (SGLT2i), have been recently developed and are now used together with the insulin therapy.

In contrast, several social issues that affect the treatment of diabetes, such as an aged society and the approaches to provide acceptable insulin therapy for elderly diabetes patients, have drawn considerable attention.

Therefore, in this JDI Updates, we focus on three recent topics that are related to insulin therapy: (i) impacts of newly developed insulin analogs; (ii) effects of oral antidiabetic agents in addition to insulin therapy; and (iii) recent social issues surrounding insulin treatment.

Impacts of newly developed insulin analogs

Recently, two new long-acting basal analogs (U-300 glargine and degludec) have become clinically available. Compared with U-100 glargine, which is a long-acting basal analog and has been widely used, both U-300 glargine and degludec showed comparable efficacy with regard to the reduction in glycated hemoglobin (HbA1c) and lower rates of hypoglycemia in patients with type 1 diabetes and those with type 2 diabetes[3].

The direct comparison of U-300 glargine and degludec in insulin-naïve patients with type 2 diabetes, named as the BRIGHT trial, was reported[4]. In the study, patients were randomized and treated for 24 weeks by either U-300 glargine (n = 466) or degludec (n = 463), and the insulin dose was titrated to fasting glucose of 80–100 mg/dL. As the results, HbA1c showed significant and comparable improvement, and hypoglycemia incidence and event rates over a period of 24 weeks were also comparable with both insulins, whereas hypoglycemia during the active titration period (0–12 weeks) was lower with U-300 glargine. Like the BRIGHT trial, there were two studies that compared the effects of U-300 glargine and degludec by cross-over study, one using continuous glucose monitoring[5] and another using flash glucose monitoring[6] in Japanese patients with type 2 diabetes. Both studies reported comparable efficacy with regard to the HbA1c reduction, and less risk of hypoglycemia or nocturnal hypoglycemia in U-300 glargine compared with degludec. There was an inquiry about the result by citing the BRIGHT trial and two real-world, propensity-matched studies termed CONFIRM (Clinical Outcome Assessment of the Effectiveness of Insulin Degludec in Real-life Medical Practice) and DELIVER (Differentiate Gla-300 clinical and Economic in Real-World Via EMR) that also compared the U-300 glargine and degludec, and reported different conclusions with regard to the incidence of hypoglycemia[7]. The authors suggested that the different results might be caused by differences in various factors, including patient characteristics, study design, background therapy and ethnicity[8]. Therefore, further investigations are necessary to evaluate the usefulness of these new insulin analogs.

Effects of oral antidiabetic agents in addition to insulin therapy

An addition of oral antidiabetic agents on top of insulin therapy is now recognized as a useful method to obtain better glycemic control and to reduce the amount of insulin used. In a meta-analysis of randomized control trials that studied the effect of dipeptidyl peptidase-4 inhibitors in addition to insulin treatment in patients with type 2 diabetes, improved glycemic control without an increased risk of hypoglycemia or weight gain compared with insulin treatment alone was reported[9]. In contrast, in a meta-analysis of randomized control trials that investigated the effect of SGLT2i in addition to insulin treatment on

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cardiovascular risk factors in patients with type 2 diabetes, better glycemic control and greater reductions of blood pressure, uric acid, bodyweight and daily insulin doses compared with insulin treatment alone were reported[10]. These effects of SGLT2i might provide beneficial effects to suppress cardiovascular events, but the increased risk of hypoglycemia, and urinary tract and genital infection related to SGLT2i should be of note. Another study compared the impacts of SGLT2i with pioglitazone when added to insulin therapy in patients with type 2 diabetes with an indirect comparison meta-analysis[11]. As the results, SGLT2i and pioglitazone achieved comparable reductions in HbA1c and fasting blood glucose, SGLT2i showed greater weight reduction, and pioglitazone achieved a higher reduction of daily insulin doses.

Recent social issues surrounding insulin treatment

An increase in the number of elderly patients with diabetes has become an important issue, especially in developed countries. The Japan Diabetes Society reported the results of a survey of severe hypoglycemia showing that 60.8% of patients who experienced severe hypoglycemia were insulin users, and their mean age was 74.0 years (Figure 1)[12]. Therefore, educating elderly diabetes patients about diabetes management, including the insulin self-injection technique and countermeasure methods for hypoglycemia, is very important. In this regard, Minami *et al.*[13] reported the usefulness of a method to evaluate the cognitive ability of elderly diabetes patients by counting the number of animal names recalled in 1 min. Lipohypertrophy at the insulin injection site is one of the causes of increased fluctuation of blood glucose levels after insulin injection, especially for long-term insulin users. Recently, insulin amyloid formation at the insulin injection site was reported to be a potential mechanism to increase subcutaneous insulin resistance[14]. In a systematic review and meta-analysis that investigated the prevalence of lipohypertrophy in insulin-treated patients, its very high prevalence (38%) was reported, again suggesting the importance of education regarding self-injection technique[15].

The three topics that were highlighted in this JDI Update teach us the importance of having a good understanding of the characteristics of various insulin formulations and non-insulin glucose-lowering agents, and proper education of the insulin injection procedure for patients of diverse backgrounds.

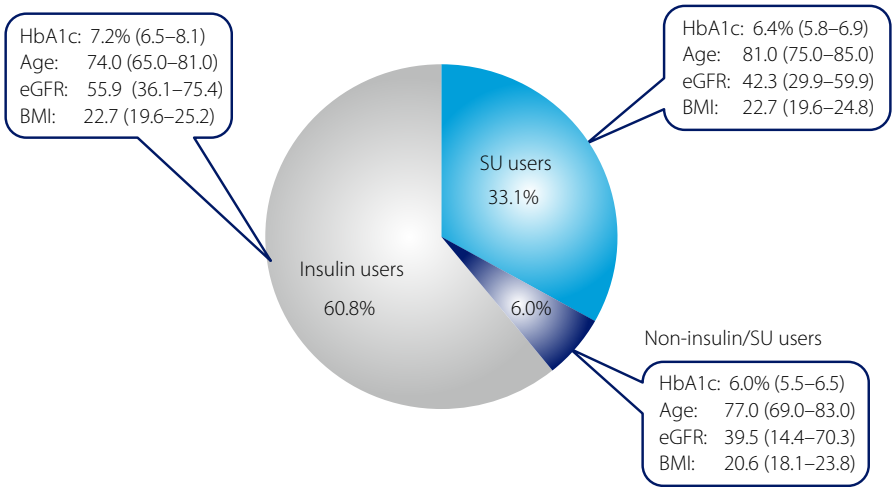

Figure 1 | Causal agents of severe hypoglycemia in Japanese patients with type 2 diabetes and their clinical characteristics. The survey of severe hypoglycemia was carried out between 1 April 2014 and 31 March 2015 in Japan by the Japan Diabetes Society Committee for the Survey on Severe Hypoglycemia[12]. Severe hypoglycemia was defined as the "presence of hypoglycemic symptoms requiring assistance from another person to treat and preferably venous plasma glucose levels at onset/diagnosis of disease or at presentation clearly <60 mg/dL (capillary whole blood glucose, <50 mg/dL)". A total of 798 case reports were collected from 113 facilities (among the 193 facilities accredited by the Japan Diabetes Society for diabetes education and provided the information), and 240, 480 and 78 patients had type 1 diabetes, type 2 diabetes and other types of diabetes, respectively. The antidiabetic agents used in patients with type 2 diabetes included insulin preparations (292 patients including 29 receiving concomitant sulfonylureas [SUs]); insulin group; 60.8%), SUs (159 insulin-naive patients; SU group; 33.1%) and no insulin preparations or SUs (29 patients; non-insulin/SU group; 6.0%). The glycated hemoglobin (HbA1c) value, age (years), estimated glomerular filtration rate (eGFR; mL/min/1.73 m^2) and body mass index (BMI; kg/m^2) of each group are shown as medians (25–75%).

DISCLOSURE

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