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Review Article

Progress in Insulin Therapy: The Impact of Basal Insulin

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ABSTRACT: This report summarizes progress in insulin products, in particular basal insulin. Prolonged, stable pharmacokinetic and pharmacodynamic profiles are very important for basal insulin, and several analog insulins for basal supplementation have been developed in the last 10 years, which has resulted in safer and more efficient glycemic control.

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KEYWORDS: diabetes, basal insulin, bolus insulin, analog insulin, hypoglycemia

Discovery of insulin

The discovery of the insulin molecule, in 1921, by Drs. Banting and Best in the United States was one of the most important events in science. Discovery of insulin dramatically changed the lives of people with diabetes. Before the discovery of insulin, type 1 diabetes was fatal because there was no way to avoid ketoacidosis, an invariably fatal complication in the absence of insulin. After the discovery of insulin, diabetes became a disease of complications.

History of insulin products

Surprisingly, only 2 years after the discovery of insulin, insulin products were commercially available, even in Japan. Many insulin products were subsequently developed, and the history of their availability in Japan is shown in Fig. 1.

Initially, only porcine and bovine insulins were available and had to be purified from the pancreas of these animals. Genetically produced human insulin became available 55 years later and does not require purification from pancreatic tissue. Moreover, the availability of human insulin enables production of stable, safe, and cheap insulin products. In the author's opinion, the most important point in the history of insulin development was the invention of the insulin analog, at the beginning of the 21st century, because the most important issue in insulin therapy at that time was to produce faster or longer-acting insulins.

Development of ultra-rapid-acting insulins

Human insulin exists as a hexamer in dilution solution. When human insulin is injected subcutaneously, it dissociates into a dimer and then a monomer and is absorbed into capillaries.[1] This process takes more than 30 minutes; thus, postprandial glucose excursions cannot be managed with such insulins. Ultra-rapid-acting insulin, which was launched in 2001, does not form dimers.[1] Instead, it quickly forms monomers and is absorbed into capillaries

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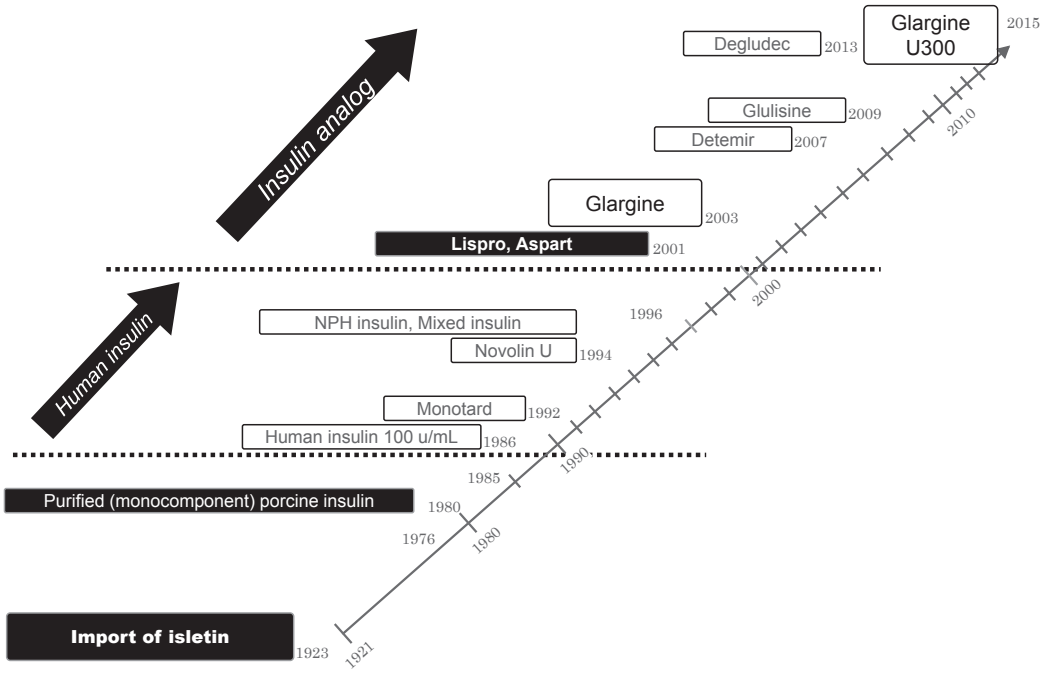

Fig. 1 Launch history of insulin products in Japan
NPH: neutral protamine hagedorn

after subcutaneous injection. Insulin concentration immediately increases and normalizes postprandial glucose elevation.[2] The time–action profiles of human regular insulin and ultra-rapid-acting insulin have been previously discussed.[2] The ultra-rapid-acting insulin aspart acts at a higher maximum concentration, with earlier timing and shorter duration as compared with regular insulin.

Because of the time–action profile of ultra-rapid-acting insulin, many physicians expected it to improve glycemic control in many people with diabetes. Postprandial hyperglycemia, which could not be managed with regular insulin, could finally be addressed. However, many physicians grew discouraged after their clinical experience with the novel insulin analog. When ultra-rapid-acting insulin replaced regular insulin in patients utilizing basal and bolus therapy with regular insulin and neutral protamine hagedorn (NPH) insulin (which acts for almost 14 hours; Fig. 2a, b), there were 3 gaps in insulin coverage, *i.e.*, before lunch, dinner, and bedtime. This uneven profile increased glucose instability and worsened glycemic control. To avoid the disadvantages of this regimen, an additional, early-morning, injection of NPH insulin was required (Fig. 2c). The need for 5 injections per day was burdensome for patients and physicians, and ultra-rapid-acting insulin was thus not commercially successful until the launch of the next analog insulin.

Development of ultra-long-acting insulins

Two years after the launch of ultra-rapid-acting insulin, an ultra-long-acting basal insulin "insulin glargine" became available for clinical use. Glucose clamp studies showed that NPH insulin, the main basal insulin, reached peak activity at 7–8 hours after injection, but that the time–action curve for insulin glargine was very flat and much longer (almost 24 hours) than that of NPH.[3]

Riddle et al compared the mean frequency of hypoglycemic episodes during the 24 hours after injection of insulin glargine or NPH insulin at bedtime in patients also using oral diabetic drugs.[4] Because of its long, flat time–action profile, insulin glargine resulted in significantly fewer hypoglycemia episodes at night. The profile of insulin glargine allows patients to decrease the frequency of basal insulin injection, as compared with NPH and to choose ultra-rapid-acting insulin as bolus insulin (Fig. 2d).

Concomitant use of ultra-long-acting insulin made ultra-rapid-acting insulin much more effective and safer.[5]

Change in basal insulin regimen

Previous studies compared the efficacy and safety of regimens starting with bolus insulin, basal insulin, or

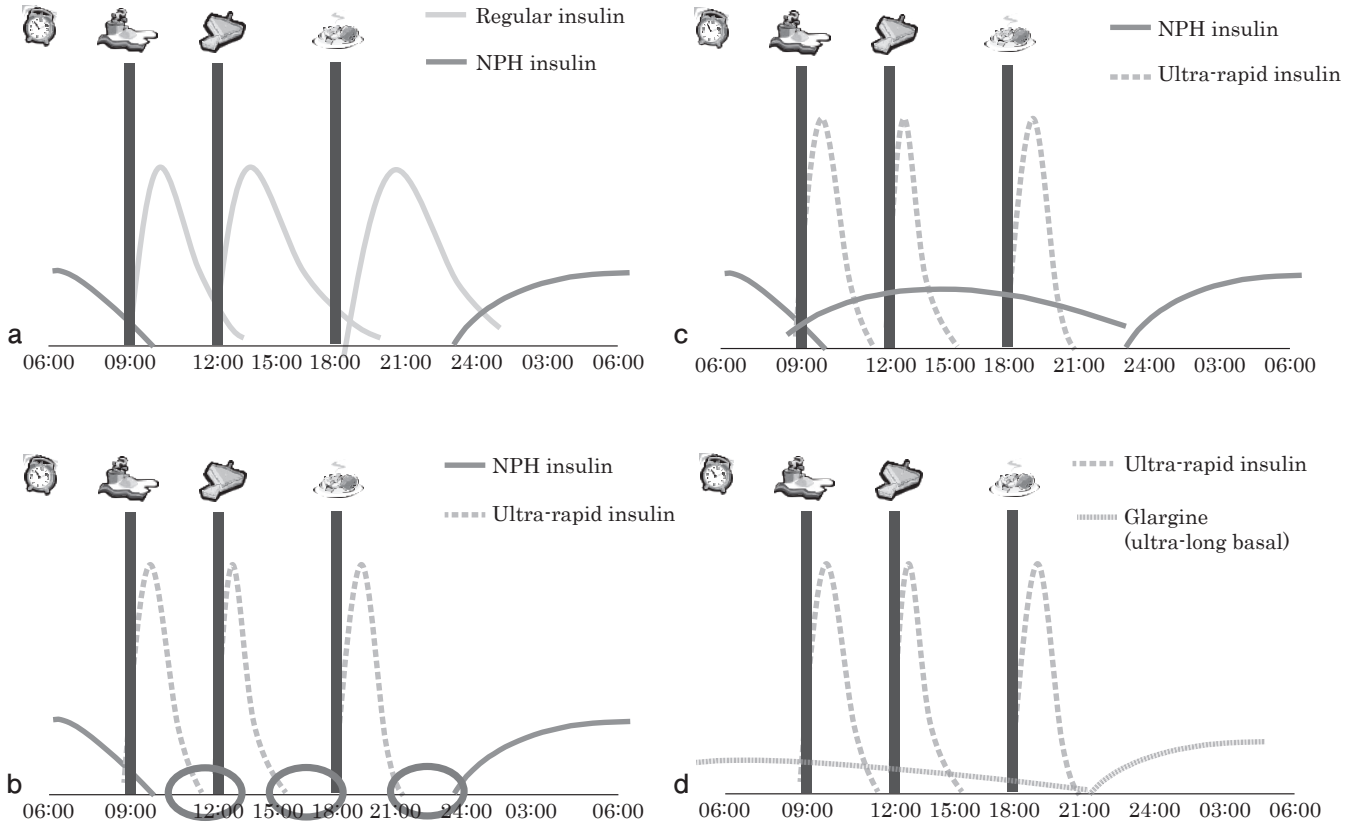

Fig. 2 Basal–bolus insulin therapy with combination of human insulin or analog insulin.
a: Basal–bolus therapy (BBT) with regular and neutral protamine hagedorn (NPH) insulins
b: BBT with ultra-rapid-acting and NPH insulins
c: BBT with ultra-rapid-acting insulin and twice-daily NPH insulin
d: BBT with ultra-rapid-acting insulin and insulin glargine

biphasic insulin for people with type 2 diabetes that was inadequately controlled by metformin and/or sulfonylurea therapy.[6, 7] One year after starting insulin treatment, another insulin was added if glycated hemoglobin (HbA1c) exceeded 6.5%. More than 80% of patients in the basal insulin group and bolus insulin group were stepped up to a basal and bolus regimen by adding bolus or basal insulin, respectively. Mean glycated hemoglobin level was similar (6.8%), but the frequency of hypoglycemia was lower, and there was less increase in body weight, among patients who started first with basal insulin.

Does increasing the ratio of basal insulin without changing total daily dose affect the safety of glycemic control?

To determine whether the above results of the Treating to Target in Type 2 diabetes (4T) study were applicable to Japanese with type 2 diabetes, we studied the effects of altering the basal-to-total insulin dose ratio on frequency of hypoglycemia and glycemic control in Japanese with type 2 diabetes receiving basal bolus insulin therapy.[8] Total daily insulin dose was unchanged. Patients with similar background characteristics were randomly allocated to 1 of 2 groups. Basal-to-total insulin dose ratio was increased over a period of 24 weeks in 1 group (Fig. 3a, b).

During the 24 weeks of the intervention, the basal-to-total insulin dose ratio remained constant in the control group, but in the intervention group the ratio was increased to 0.5 (*i.e.*, the doses of basal insulin and bolus insulin were almost identical) without increasing the frequency of hypoglycemia. As the basal-to-total insulin dose ratio was increased, mean glycosylated albumin (GA) was significantly lower in the intervention group at 20 and 24 weeks than in the control group, even though the total daily insulin dose was identical in the groups (Fig. 4). These findings suggest that patients with type 2 diabetes should receive the maximum possible dose of basal insulin,

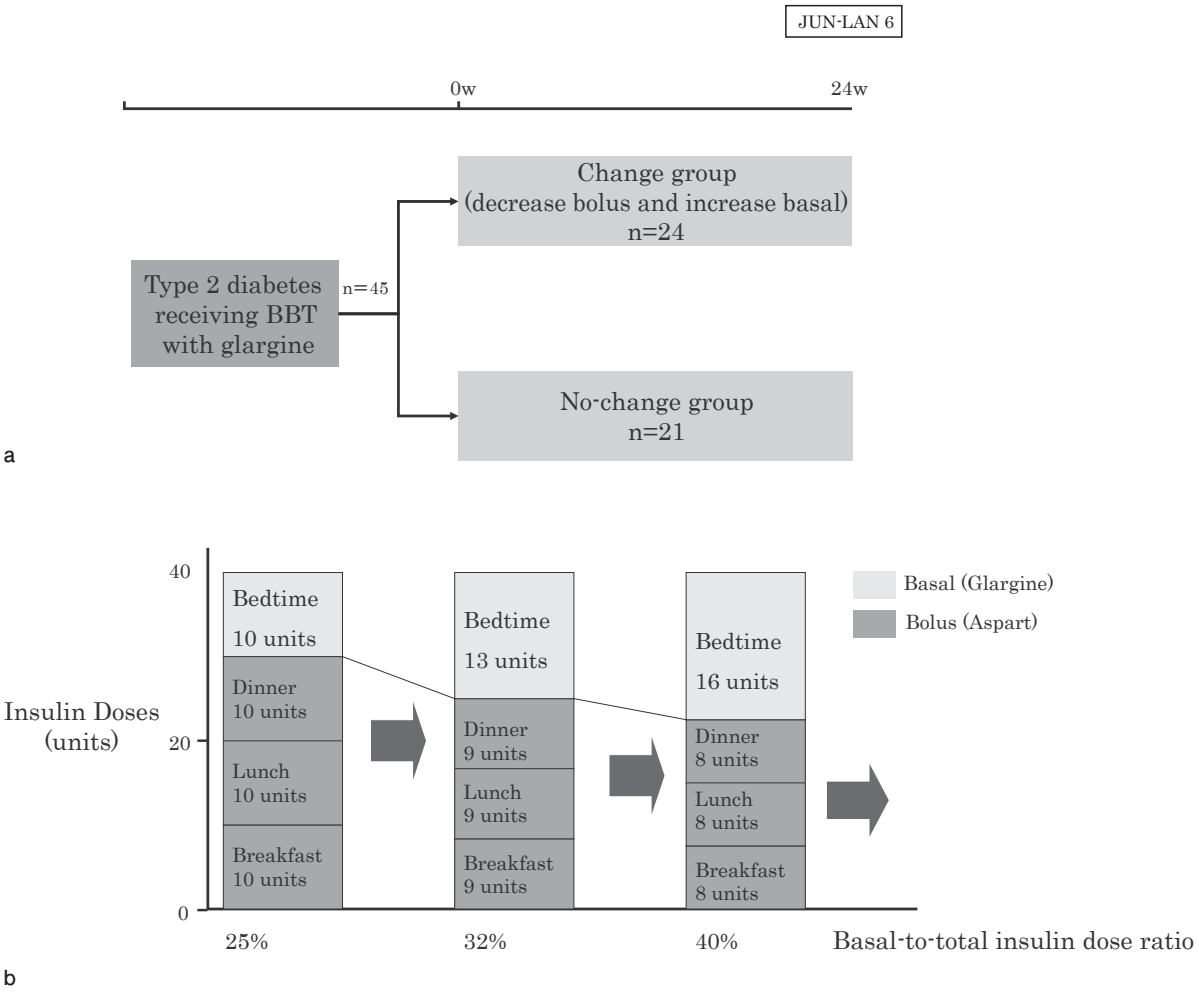

Fig. 3
a: Study of effect of increasing basal insulin dose without increasing total daily dose
b: Change in basal-to-total insulin dose ratio in type 2 diabetes patients receiving basal–bolus therapy (BBT)

to improve glycemic control without increasing hypoglycemia frequency.

Launch of novel ultra-long-acting insulin

Although insulin glargine has a long duration of action, gaps in basal supplementation are still frequent especially in case when this insulin is injected once daily in the morning. For this reason, longer-acting basal insulins are desirable, and 2 such basal insulins were launched recently. Insulin degludec (IDeg) was launched in 2013 and has a mean half-life of 25.4 hours (the half-life of glargine is 12.5 hours).[9, 10] IDeg is active for almost 42 hours, much longer than insulin glargine (24 hours). IDeg is a formulated insulin analog of dihexamers that reorganize into a multihexamer in injected subcutaneous tissue.[11] The multihexamers slowly degrade to monomers, which are then readily absorbed into systemic circulation.[11]

Another novel basal insulin is insulin glargine 300 U/ml (Gla-300), which has more-stable and prolonged pharmacokinetic and pharmacodynamic profiles in comparison with the original insulin glargine 100 U/ml (Gla-100). In addition, glycemic control persists longer than 24 hours in people with type 1 diabetes. These basal insulins, which are active for longer than 24 hours, have no deficiencies in their time–action profiles and thus result in stable and efficient glycemic control.[12–17]

LY2605541 is novel "PEGylated" basal insulin. Insulin lispro is a 5.8-kilodalton (kDa) peptide hormone. Polyethylene glycol (PEG) is a neutral linear polymer, which is conjugated to insulin lispro to produce basal analog LY2605541. It is able to bind 3 molecules of water, allowing it to become highly hydrated, thereby increasing the hydrodynamic size of the molecule, which delays

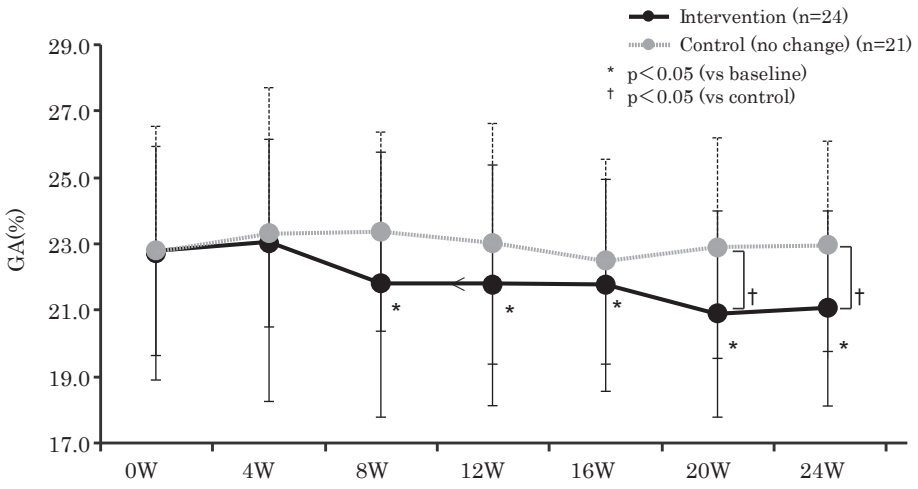

Fig. 4 Mean change in glycosylated albumin (GA) in type 2 diabetes patients receiving basal and bolus therapy with insulin glargine

absorption and reduces renal filtration, thus greatly extending the half-life of LY2605541. PEGylation also protects against proteolytic degradation. PEGylation is novel in the context of insulin, but is a well-established strategy to improve the therapeutic properties of proteins. It is probably absorbed via lymph tissues rather than by capillaries, after which it enters vessels. Very little reaches the regular target organs of insulin, such as skeletal muscle, due to the size of the compound. However, the liver has large holes in the tissue surface, through which this insulin can work. For this reason, LY2605541 may prove to be a unique and preferential hepatospecific insulin analog.[18–23]

After this lecture was given, on November 13, 2015, a phase III study of LY2605541 in United States was suspended because of adverse reactions, *i.e.*, elevation of alanine aminotransferase.[24]

Conclusion

The ideal basal insulin would have a long, flat, and predictable time–action profile and act via both muscle and liver. Future insulin research and development should focus on these characteristics.

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Takahisa Hirose, Professor Curriculum vitae

March	1985	Graduated from Osaka Medical College, and passed the National Examination for Medical Practitioners
May	1985	Intern, Department of Internal Medicine, Osaka University
July	1986	Medical staff, Department of Internal Medicine, Kinki Central Hospital of the Mutual Aid Association of Public School Teachers
March	1992	Ph.D. degree granted, Department of Internal Medicine, Osaka University Graduate School of Medicine
April	1992	Postdoctoral fellow, National Institute of Environmental Health and Sciences, National Institutes of Health (North Carolina, USA)
April	1995	Postgraduate, Department of Internal Medicine, Osaka University
June	1997	Assistant Professor, Department of Internal Medicine, Osaka University
August	1997	Chief Physician, Nishinomiya Municipal Central Hospital
April	2004	Assistant Professor, Division of Metabolism and Endocrinology, Department of Internal Medicine, School of Medicine, Juntendo University
April	2006	Associate Professor, Division of Metabolism and Endocrinology, Department of Internal Medicine, School of Medicine, Juntendo University
April	2012	Professor, Division of Diabetes Metabolism and Endocrinology, Department of Internal Medicine, School of Medicine, Faculty of Medicine, Toho University

Awards

NIH Research Award (1994), etc.

Specialty Areas

Study of clinical endocrinology, basic clinical research on nuclear receptors, clinical diabetology, medical treatment, insulin treatment (outpatient insulin initiation), etc.

Memberships and Certifications

Board Certified Member of the Japanese Society of Internal Medicine, Japan Endocrine Society (Medical specialist, Advising doctor, Academic councilor), Japan Diabetes Society (Medical specialist, Advising doctor, Academic councilor), Japan Medical Association (Certified Occupational Health Physician)