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Editorial

What to know about insulin treatment?

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Diabetes Mellitus is a chronic and complex disease with glycemic control at the center of its treatment and requires continuous monitoring and treatment of complications. Clinical studies such as DCCT/EDIC and UKPDS have shown that proper glycemic control is effective in preventing early and late complications of diabetes.[1-4] Insulin therapy is a critical part of treatment for people with type 1 diabetes and also for many patients with type 2 diabetes.

Type 1 Diabetes

In type 1 diabetes, there is no insülin production at all due to the autoimmune destruction of beta cells.[5] Since 1923, insulin has been a lifesaving miracle drug in the treatment of type 1 diabetes. Patients with type 1 diabetes generally needs multiple daily insulin injection from the onset of the disease.

Two types of insulin, long/longer-acting (basal) and rapid-acting (bolus), are used in the intensive treatment that called basal-bolus regimen .[6,7] While, basal insulin provides glycemic control between meals, rapid-acting analog insulin that administered just before the meals control post-prandial hyperglycemia. Studies have shown that long-acting insulins have better effects on glycemic control and have lower risk of hypoglycemia.[8-11]

Initially, the total daily insulin requirement is determined between 0.4-1.0 IU/kg/day according to the patient's metabolic status and weight. In patients with stable metabolic status 0.5 IU/kg/day is usually preferred as the initial dose.[6,12] Half of the calculated daily dose is administered as a basal insulin, while the other half is divided into three and administered before each meals as a bolus injection.[13,14] In patients with a healthy lifestyle, if hypoglycemia occurs during fasting in the morning, basal insulin dose should be reviewed, and bolus insulin dose should be reviewed if it occurs at 2 hours after meal.

Following the initial dose recommended in the guidelines, the individual insulin dose that required by the patient should be determined as soon as possible with intensive blood glucose monitoring. The diet and individualized insulin dose titration according to the efficacy characteristics of the selected insulin should be dynamically performed just after starting insulin treatment. Fasting blood glucose measurements are important to determine basal insulin dose and post-pandial blood glucose levels are necessary for the judgment of bolus insulin dose. Post-prandial blood glucose levels are directly related to the meal ingredients. Patients' training on nutrition-based insulin dose adjustment is crucial to sustain daily life.[15-17]

Learning carbohydrate counting is essential for the patients to assume required bolus insulin dose.[18]

Type 2 Diabetes

In patients with type 2 diabetes, initially, beta-cell usually have insulin synthesis and secretion disorders, as well as insulin resistance in peripheral tissues such as liver, skeletal muscle, adipose tissue, and brain.[19]

In these patients, oral antihyperglycemic

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treatment is applied primarily to provide glycemic control.[17, 20] In patients who can not maintain adequate glycemic control with oral antihyperglycemic combination therapies, combination with basal insulin or GLP-1 analogs are considered as the most appropriate treatment.[21,22]

Since insulin has the advantage of being effective when other agents are not effective in type 2 diabetes, it should be considered to include it in oral therapy in the presence of severe hyperglycemia symptoms such as weight loss and ketosis.[23] There are studies showing that glycemia can be controlled better, and the risk of hypoglycemia is lower by using longer-acting insulins as basal insulin.[24-29] It has been reported that glycemic control is very successful, and weight gain and hypoglycemia risk are low in type 2 diabetic patients with long-acting basal insulin and GLP-1 combined preparations, which have been used in recent years.[30-34]

Many patients with type 2 diabetes require insulin treatment over time. Patients with type 2 diabetes should be explained in simple language that insulin treatment may be needed over time due to the progressive nature of the disease, which is a normal process for this disease.

Insulin therapy should be considered as the initial treatment in patients with type 2 diabetes with a blood glucose of 300-350 mg/dl and/or HbA1c 10-12%. When combination therapy with insulin is required in the treatment of oral antidiabetic agents in type 2 diabetes, it is recommended to add basal insulin therapy in the first step. Basal insulin starting dose is 10 IU/day or 0.1-0.2 IU/kg/day depending on the degree of hyperglycemia.

After starting insulin treatment with the initial dose that recommended in the guidelines, actual personalized dose of the patient should be determined as soon as possible. Basal insulin dose adjustments are made every 3-4 days until fasting glycemia levels reach the target value. In patients with a healthy lifestyle, if morning fasting hypoglycemia occurs, the switch of basal insulin to oral agents should be evaluated. If dose adjustments were not applied, and the treatment with initial doses continued, most of the patients will remain in poorly controlled conditions with insufficient doses of insulin for many years.

It is not recommended to stop oral antihyperglycemic agents when basal insulin therapy is initiated, unless there is a contraindication. Due to the water-retaining effect of pioglitazones, patients' condition should be evaluated carefully before the addition of basal insulin to previous therapy which already had the water-retaining effect. Metformin is usually added into the combination with basal insulin therapy.

Post-prandial glucose elevations should be considered after fasting glycemia has reached target levels with basal insulin titration, but HbA1c levels persist above the target.[6] When basal insulin doses are >5 IU/kg/day, the addition of bolus insulin to the most intense meal or a combination with a GLP-1 analog should be considered.[6] Options include a GLP-1 receptor analog or the addition of bolus insulin prior to the most substantial meal of the day. Since the effects of rapid-acting analog insulins begin within a few minutes, they are used as a bolus to prevent hyperglycemia after meals.[35-37]

If one basal and one bolus insulin treatment is not sufficient, GLP-1 receptor agonist or bolus insulin may be added to the other meals.[38,39] In patients with type 2 diabetes, prandial insulin is usually started at 4 IU or 10% of the basal dose.[6]

While insulin doses are personalized, basal insulin dose should be monitored with fasting glycemia in the morning, and bolus doses should be regulated with the glucose monitoring 2 hours after meal.

Premixed insulins are preferred less because of the risk of hypoglycemia.[6] Although 2-3 doses of premixed (biphasic) insulin treatments are cheap, they can only be used in patients with low risk of post-prandial hypoglycemia.

Insulint types in market are listed in Table 1.

Continuous subcutaneous insulin pumps

Subcutaneous pumps have been used as an alternative to basal-bolus insulin treatment, although they are costly. These pumps use rapid-acting insulins, and the basal insulin requirement is met automatically by the pump at frequent intervals throughout the day, and the bolus insulin requirement is determined by the patient based on the condition of the meal to be taken. In meta-analysis studies comparing subcutaneous continuous insulin pumps with basal-bolus treatment, there was a slight difference in the reduction of HbA1c levels and in favor of pump therapy.[40]

For the last two years, hybrid closed-loop

Table 1. Insulin types in use

		Action start time	Peak time	Action duration time
Prandial (bollus) insulins				
Short-acting human Recombinant DNA	Human regular	30-60 min.	2-4 hours	5-8 hours
Rapid-acting analogs	Glulisine Aspart Lispro	15 min.	30-90 min.	3-5 hours
Basal insulins				
Intermediate-acting	Human NPH	1-3 hours	8 hours	12-16 hours
Long acting	Glargine U-100 Glargine U-100 biosimilar Detemir	60-90 min.	No peak	20-26 hours
Longer acting	Glargine U-300 Degludec U-200	6 hours 2 hours	No peak No peak	30 hours 40 hours
Premixed insulins				
NPH/Regular, %	70/30	30-60 min.	Changing	10-16 hours
NPL/Lispro, %	75/25 or 50/50	10-15 min.	Changing	10-16 hours
NPA/Aspart, %	70/30 or 50/50			
Degludec/Aspart, %	70/30	10-15 min.	Changing	40 hours
Premixed insulin/GLP-1 RA				
Glargine /Lixisenatide	Glargine U-100 20 or 30 IU/ Lixisenatide 10 μg.	60-90 min.	No peak	30 hours

pumps have been used in the USA to regulate both basal and bolus insulin doses throughout the day [41-43]

Inhaled Insulins

Inhaled insulins have been introduced to control postprandial glycemia. After starting treatment with these insulins, continuous monitoring of lung function is required about mouth, throat, upper respiratory tract, and lung problems.[44]

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