Insulin Analogs Applied with Continuous Subcutaneous Insulin Infusion (Pump) in the Treatment of Diabetes
Devamlı Subkütan İnfüzyon (Pompa) ile Uygulanan İnsülin Analoğlarının Diyabet Tedavisindeki Yeri

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Abstract
Diabetes mellitus (DM) is an important health problem that should be treated efficiently because of its high prevalence and high morbidity and mortality due to its complications. In patients with DM, the application of a treatment which provides physiologic insulin secretion as such in healthy individuals is directly related with the prevention of diabetes complications. Insulin analogs, which were developed in recent years and shown to have pharmacokinetic and pharmacodynamic superiority to human insulin, have made it possible to obtain natural insulin pattern in the body. In addition to development of insulin analogs, introduction of insulin application method of "continuous subcutaneous insulin infusion" insulin pump has led a new era in the treatment of DM. In this review, treatment of type 1 and 2 DM patients with insulin analogs, particularly insulin aspart, applied with insulin pump was discussed in the light of the current literature. Turk Jem 2015; 19: 19-24

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agents i.e. insulin glargine and insulin detemir are developed as basal insulins, and the rapid-acting insulin analogues, e.g. insulin lispro, insulin aspart and insulin glulisine are developed as bolus insulins [5]. Introduction of insulin analogs has greatly improved the clinical treatment of type 1 and type 2 DM [6]. The application of a physiological level of insulin in DM patients is directly related to prevention of complications. Continuous subcutaneous insulin infusion (CSII) is the most physiological way to administer insulin and has been available for more than 30 years, and has opened a new era in the treatment of diabetes together with analogue insulins [7,8]. It is estimated that there are approximately 500,000 insulin pump patients worldwide [9]. In this review article, insulin analogues, particularly insulin aspart, delivered with a pump in the treatment of patients with type 1 and type 2 DM was discussed in the light of the current literature.

Exogenous Insulin Treatment

Exogenous insulin therapy is essential in type 1 DM and becomes a necessity in patients with type 2 DM who have reduced beta cell function and fail to achieve optimal control with oral hypoglycemic agents. In patients with DM and deficiency of endogenous insulin production, exogenous insulin regimen will be designed to stimulate insulin secretory responses present in normal subjects in order to enable targeted glycemic control. Exogenous insulin therapy enhances glycemic control, reduces the risk of long-term vascular complications, minimizes short-term crises, and leads to improved quality of life [10]. To achieve this, continuous basal insulin level with additional boluses at meals should be considered. Two commonly used approaches for initiating insulin therapy are the addition of intermediate- or long-acting insulin preparations (i.e. NPH, human insulin, insulin glargine, insulin detemir) to oral therapy, and the initiation of treatment with premixed insulin [11]. The long-acting insulin analogues do not have a pronounced “peak” effect as NPH insulin, and are supposed to cause less hypoglycemia, mainly during the night [12,13]. The newly developed insulin analogues were designed to provide more physiologic, pharmacokinetic and pharmacodynamic properties compared with human insulin, and to imitate the body’s natural physiological secretion of insulin [11]. Studies have shown that short-acting insulin is absorbed faster and offer a more rapid onset of action and shorter duration of activity than human insulin [14]. Therefore, insulin aspart significantly improves postprandial blood glucose control [15]. Furthermore, use of insulin aspart results in a lower risk of major hypoglycemia compared to human insulin [11,16]. Because of these features, short-acting insulins can be injected before or immediately after a meal.

Exogenous Insulin Application Methods

While clinical studies on inhaled, intranasal and topical forms of insulin are still ongoing, there are currently two treatment regimens that mimic the profile of endogenous insulin in DM patients: CSII (insulin pump therapy) and multiple daily injections (MDI) [17]. CSII consists of the pump, an infusion set, and a syringe. Insulin pens may be prefilled (disposable) or reusable [9]. The pump is programmed to infuse short-acting insulin continuously at a basal rate. The patient can adjust the basal rate if circumstances require a temporary increase or decrease in insulin. The patient also needs to activate the pump to administer a bolus dose of insulin at mealtimes, and to decrease insulin dose prior to the planned exercise to prevent hypoglycemia. CSII therapy offers a more precise physiological method of insulin administration. Since insulin pumps can be useful in mimicking the physiological insulin secretion, and major hypoglycemia attacks are abated with insulin administration by insulin pumps, they have been increasingly used in type 1 and type 2 DM patients.

The Advantages of Insulin Pumps

As mentioned above, insulin pumps allow a close to physiologic insulin delivery. Insulin pump therapy offers similar or better improvement in glycemic control with less major hypoglycemia compared to MDI [7,8]. With a pump, the basal insulin level can be adjusted and fine-tuned to closely match the body’s needs. In addition, pump wearers have a better quality of life and patient satisfaction compared to those on insulin injections. In their study, DeVries et al. [18] compared insulin aspart administered by infusion pump with insulin aspart plus NPH injection in type 1 DM patients. They used the 36-item Short Form Health Survey (SF-36) to assess quality of life, and general and mental health scores were found to be significantly higher in the insulin pump group. In a study by Raskin et al. [19] performed with type 2 DM patients, similar results were obtained, and patient satisfaction was reported to be significantly higher in patients using an insulin pump compared to those using insulin injections.

A study, aiming to compare quality of life and treatment satisfaction by using the Diabetes-Specific Quality-of-Life Scale (DSQOLS), Diabetes Treatment Satisfaction Questionnaire (DTSQ) and SF-36 in 1341 type 1 DM patients suggested greater lifestyle flexibility, less fear of hypoglycaemia, and higher treatment satisfaction, when continuous subcutaneous insulin injection is compared with multiple daily injection regimens [20]. In addition to the parameters including efficacy, safety, quality of life and patient’s satisfaction, pump insulin administration has also been reported to be cost-effective versus multiple daily injection regimens in patients with type 1 DM [21]. Table 1 lists the advantages of insulin pump therapy. The results of clinical studies on safety and effectiveness of insulin pump therapy in patients with type 1 DM are summarized below.

Insulin Pump Therapy in Type 1 Diabetes Mellitus

There have been several studies investigating the application ways of insulin in type 1 DM patients who lack endogenous insulin. In a cross-sectional study of 79 type 1 DM patients, pump insulin administration was compared to insulin aspart plus NPH for 32 weeks, and the mean HbA1c decrease was found to be significantly higher in the insulin pump group (-0.91±1.28% and -0.07±0.70%, respectively, p=0.002) [18]. Blood glucose stability assessed by 9-point blood glucose profile was observed to be significantly improved in insulin pump group. In another similar
study, CSII with insulin aspart versus multiple daily injection therapy of insulin aspart plus insulin glargine was compared in 100 type 1 DM patients (22). In this study, the mean blood glucose level was significantly lower in the insulin pump group. Monami et al. (23) mentioned in their meta-analysis of 11 randomized clinical trials comparing at least 12 CSIs versus multiple daily injection therapy of insulin that insulin pump therapy provided a significant improvement in HbA1c (mean standardized difference: -%0.3 [95% confidence interval: %0.4/0.1], p<0.001), and that no significant difference was observed between the two groups regarding major hypoglycemia. A randomized, cross-sectional study in which basal insulin substitution with glargine was compared to basal insulin substitution with insulin pump using insulin aspart or insulin lispro in type 1 DM patients has shown that insulin administration via a pump provided better blood glucose control compared to insulin glargine, and the required dose of insulin was lower (24). In a study conducted in 50 type 1 DM patients in our clinic, a decrease of 0.79% in HbA1c in a median follow-up of 1.66 years was detected in 27 patients who have put on insulin pump therapy; and hypoglycemia incidence was also found to be lower (25). Furthermore, type 1 DM patients using insulin pump declared higher satisfaction compared to those on basal bolus insulin (25). A meta-analysis of 165 pediatric type 1 DM patients, which compared insulin pump therapy versus multiple daily injections, suggested that participants using insulin pump had significantly lower HbA1c levels and a lower insulin requirement than those using MDI (26). Another meta-analysis of 22 randomized studies comparing frequency of major hypoglycemia in two different insulin delivery methods showed that those treated with insulin pump therapy had 2.89 times lower frequency of major hypoglycemia than those receiving multiple injection (95% confidence interval: 1.45/5.76) (27).

Considering these previous clinical studies, patients with type 1 DM who used an insulin pump achieved better blood sugar control, lower frequency of hypoglycemia, better quality of life and patient satisfaction than patients who used the standard treatment of insulin injections.

### Insulin Pump Therapy in Type 2 Diabetes Mellitus

The number of studies conducted in type 2 DM patients to compare insulin pump therapy with MDI is less than research on type 1 DM patients (28). In a randomized, open-label study of 132 type 2 diabetic patients, a decrease in HbA1c values and 24-hour blood glucose profile was observed in both groups of patients treated with insulin aspart in a pump system or multiple injections of insulin aspart plus NPH. In addition, plasma lipid levels and frequency of hypoglycemia were similar, and both treatment regimens had similar efficacy and tolerability (19).

A retrospective study over a 24-month period in patients receiving insulin pump therapy has shown that insulin pump therapy was safe and effective for maintaining glycemic control, higher benefit was seen in patients with HbA1C levels above 8% at baseline, and this effect continued throughout the six-year follow-up period (29). Two studies conducted among people over 60 years of age to compare pump and injection systems for insulin revealed that both methods provided good glycemic control, glucose change, safety and patient satisfaction (30,31).

Researchers performed a meta-analysis of four randomized studies to make a direct comparison of pump therapy and daily injection of insulin in type 2 DM patients and found that the effect on HbA1c was similar in both groups (mean standardized difference: 0.09% [95% confidence interval: %0.08/0.26], p=0.31). The number of hypoglycemic episodes was not different between the groups (32). Available data from the limited number of studies examining the outcomes of type 2 DM patients demonstrated that pump and injection systems for insulin produced similar glycemic efficacy and hypoglycemia risk.

### Insulin Preparations Used in Insulin Pump Therapy

Before insulin analogues were available, only soluble human insulin had been used with a subcutaneous insulin infusion pump. Nowadays, besides human insulin, short-acting human insulin analogues insulins lispro, insulin aspart, and insulin glulisine produced by recombinant DNA technology are also given via insulin pump (33). Insulin analogues provide better glycemic control, achieve less hypoglycemia, reduce postprandial glucose excursions, and lead to better patient compliance, quality of life and treatment satisfaction (34). Figure 1 shows the transition of patients to insulin pump treatment.

### Human Insulin

The production of human insulin via the recombinant DNA technique includes insertion of the human proinsulin gene into either Saccharomyces cerevisiae or a non-pathogenic strain of Escherichia from which human insulin is isolated and purified. Regular human insulin has a delayed onset and long duration of action leading to postprandial hyperglycemia, late hypoglycemia, impaired quality of life, poor compliance, and abnormal glucose regulation.

### Insulin Glulisine

Insuline glulisine which is a rapid acting insulin analogue, has lysine at position B3 and glutamic acid at B29 instead of asparagine and lysine in human insulin, respectively (Figure 2). The onset of action of insulin glulisine injected subcutaneously is more rapid, and the duration of action is shorter compared to regular human insulin. Insulin pumps may be used to apply insulin glulisine.
**Insulin Aspart**

Insulin aspart, a rapid-acting human insulin analog is prepared by replacing the amino acid in the B28 position, proline, by aspartic acid (Figure 2). This chemical structure leads to rapid onset of action.

**Insulin Lispro**

Insulin lispro is an analog of human insulin created when the amino acids at positions 28 (proline) and 29 (lysine) of the B-chain of insulin are reversed. Insulin lispro maintains more rapid absorption when compared to soluble human insulin, becomes active about 15 minutes after injection (Figure 2). Since it is absorbed faster than human regular insulin, time to peak is faster, the duration of action shorter, and has a decreased risk of hypoglycemic episodes. Insulin lispro shows similar pharmacokinetic properties to insulin aspart, and 40 minutes faster decline in free insulin concentration from peak concentration to 50% of the maximum concentration (113±10 and 154±14 minutes, respectively) (35). The pharmacokinetic properties of short-acting insulin analogues, such as insulin lispro, insulin aspart and insulin glulisine are summarized in Table 2.

**Comparative Clinical Studies with Insulin Analogues**

Although insulin aspart and lispro have identical in vivo potency compared to regular human insulin, short-acting insulins achieve higher peak concentrations. In a pharmacokinetic study by Homko

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**Table 2. Comparison of pharmacokinetic properties of three rapid-acting insulin analogues-aspart, lispro, and glulisine (40)**

<table>
<thead>
<tr>
<th></th>
<th>Insulin Lispro</th>
<th>Insulin Aspart</th>
<th>Insulin Glulisine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to onset of action</td>
<td>15 min</td>
<td>15 min</td>
<td>15-30 min</td>
</tr>
<tr>
<td>Peak time (hour)</td>
<td>0.5-1.5</td>
<td>1-3</td>
<td>0.5-1</td>
</tr>
<tr>
<td>Duration of action (hour)</td>
<td>2-4</td>
<td>3-5</td>
<td>4</td>
</tr>
<tr>
<td>Distribution</td>
<td>Vd. 0.26–0.36 L/kg</td>
<td>Binding to plasma proteins: 0%–9%</td>
<td>Vd. 13 L</td>
</tr>
<tr>
<td>Elimination</td>
<td>Half life: 60 min</td>
<td>Half life: 81 min</td>
<td>Cl. 1.22 L/hour/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Half life: 13 min (iv/42 min (sc))</td>
<td></td>
</tr>
</tbody>
</table>

min: minute, Vd: volume of distribution, Cl: clearance rate, iv: intravenous, sc: subcutaneous
et al. (36) type 1 DM patients received subcutaneous injections of either aspart or lispro and both insulin analogs produced similar serum insulin levels, and had similar effects on glucose and fat metabolism. Plank et al. (37) showed in their study that the pharmacokinetic and pharmacodynamic profile of insulin aspart was similar to insulin lispro, and both insulin analogs were equally effective for control of postprandial blood glucose.

A randomized, open-label, parallel-group study comparing outcomes of type 1 DM patients (n=146) receiving either human insulin, insulin aspart or insulin lispro by pump infusion revealed that HbA1c levels were similar to basal levels after 16 weeks of treatment in all groups (changes from baseline: 0.00%, 0.15%, and 0.18%, for insulin aspart, human insulin and insulin lispro, respectively (17). On the other hand, the frequency of hypoglycemia was found to be significantly lower in the insulin aspart group than in the human insulin or insulin lispro groups. Another study conducted in 59 type 2 DM patients to compare insulin treatment with human insulin to insulin aspart, both given by pump, found that there were no differences in the frequency of hypoglycemic events between the treatment groups, insulin aspart provided better glycemic control, and the mean values for daily basal and daily bolus insulin dose were significantly lower in insulin aspart group (38).

Siegmund et al. (39) have compared insulin aspart and insulin lispro in terms of pump compatibility and the development of side effects in type 2 DM patients. The overall side effect score was found to be significantly lower in insulin aspart group patients. However, in insulin aspart group, fewer patients reported having pain and burning sensation, inflammation and rash, and at the end of the study, most patients preferred to continue with insulin aspart. A recent review by Bode (40) compared pharmacokinetic properties, physicochemical stability and pump compatibility of 3 rapid-acting insulin analogues, and reported that insulin aspart had highest physical and chemical stability and less tendency to catheter occlusion (aspart 9.2%, lispro 15.7% and glulisine 40.9%, p<0.01).

In a open-label, randomized study conducted by van Bon et al. (41) in 2011 on type 1 DM patients receiving short-acting insulin analogues (insulin glulisine, insulin aspart or insulin lispro), no difference was found between the groups in terms of hyperglycemic attacks and/or catheter occlusion, and glycemic endpoints including change in HbA1c, 7-point blood glucose profile, major hypoglycemia and symptomatic ketoacidosis. On the other hand, hypoglycemia was significantly more frequent in the insulin glulisine group than both in the insulin aspart and insulin lispro groups. Bartolo et al. found that postprandial glucose was more stable when insulin aspart was infused as a pre-meal bolus compared with insulin lispro (42).

By virtue of similar effects, decreased hypoglycemic attacks and side effect profile, insulin aspart offers advantages over other short-acting insulins.

**Conclusion**

CSII using an external pump in patients with DM is the most physiological method of insulin therapy available at present. The body of evidence suggests that CSII is better than multiple injections for glycemic control, frequency of hypoglycemia, quality of life, patient satisfaction and cost savings in type 1 DM patients. The outcomes of type 2 DM patients demonstrated that pump and injection systems produced similar glycemic efficacy and hypoglycemia risk. Further randomized studies are needed to evaluate the use of insulin pumps in patients with type 2 DM. All short-acting insulin analogues (insulin aspart, glulisine and lispro) are appropriate insulins for insulin infusion pumps. Based on the pharmacokinetics of the insulin preparations and the results of the comparative studies, insulin pump therapy may be superior to MDI in minimizing the risks of hypoglycemia and side effects. Thus, insulin aspart solution can be used with an external insulin pump in patients with type 1 and type 2 DM.
References


