DOI: 10.4274/tjem.2635

Insulin Analogs Applied with Continuous Subcutaneous Insulin Infusion (Pump) in the Treatment of Diabetes

Devamlı Subkütan İnfüzyon (Pompa) ile Uygulanan İnsülin Analoglarının Diyabet Tedavisindeki Yeri

Ercan Tuncel, Soner Cander*, Özen Öz Gül

Uludağ University Faculty of Medicine, Department of Endocrinology and Metabolism, Bursa, Turkey
*Şevket Yılmaz Training and Research Hospital, Clinic of Endocrinology and Metabolism, Bursa, Turkey

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*
Anahtar kelimeler: Diabetes mellitus, insulin infusion systems, insulin pump, insulin

Çıkar Çatışması: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemiştir.

Özet

Diabetes mellitus (DM), yüksek prevalansı ve komplikasyonlarına bağlı morbidite ve mortalite nedeniyle iyi tedavi edilmesi gereken önemli bir sağlık sorunudur. DM hastalarında, sağlıklı bireylerdeki insülinin fizyolojik salınımına yakın bir tedavi uygulaması diyabet komplikasyonlarının önlenebilmesiyle doğrudan bağlantılıdır. Son yıllarda geliştirilen ve insan insülinine farmakokinetik ve farmakodinamik üstünlüğü gösterilen analog insülinler ile vücutta doğal insülin seyrinin elde edilebilmesi mümkün hale gelmiştir. Analog insülinlerin geliştirilmesi yanında en fizyolojik insülin uygulama yöntemi olan devamlı subkütan insülin infüzyonunun ("continuous subcutaneous insülin infusion", pompa insülin), insülin uygulama şekli olarak kullanılması DM tedavisinde yeni bir dönem açmıştır. Bu derlemede, tip 1 ve 2 DM hastalarında pompa ile insülin analoglarının, ağırlıkla insülin aspartın, uygulaması güncel literatür eşliğinde tartışılmıştır. *Turk Jem 2015; 19: 19-24*
Key words: Diabetes mellitus, insülin infüzyon sistemleri, pompa insülin, insülin

Conflicts of Interest: The authors reported no conflict of interest related to this article.

Introduction

Diabetes mellitus (DM) is a chronic, progressive disease affecting 150 million people worldwide and estimated to affect 300 million by 2025 (1). In TURDEP (Turkey Diabetes, Hypertension, Obesity and Endocrinological Diseases Prevalence Study) study from Turkey in 1997-1998, the prevalence of diabetes in subjects over 20 years of age was found to be 7.2%, and in a repeat study of TURDEP II conducted ten years later, the prevalence had almost doubled and increased to 13.7% (7.5 new cases). Then, according to 2010 data, there are about 6.4 million DM patients in Turkey (2). As the prevalence of this disease increases, morbidity and mortality risks associated with diabetes and its complications also increase. Therefore, early diagnosis and appropriate treatment of DM are very important. The risk of long-term complications, such as cardiovascular death, retinopathy and nephropathy can be reduced by improved glycemic control if glycosylated hemoglobin (HbA1c) is maintained below 7% (3).

Insulin is indicated in all type 1 DM patients and also in type 2 diabetics when adequate glycemic control cannot be achieved by nondrug measures and oral antidiabetic medications. However, it is no possible to replicate the pattern of basal and postprandial endogenous secretion of insulin with conventional insulins including regular human insulin and intermediate-acting neutral protamine Hagedorn [NPH] insulin (4). (*) Thus, the long-acting

Address for Correspondence: Soner Cander MD, Şevket Yılmaz Training and Research Hospital, Clinic of Endocrinology and Metabolism, Bursa, Turkey
E-mail: drcander@gmail.com **Received:** 17/07/2014 **Accepted:** 02/10/2014

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 meal(s) 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 a 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 CSIIs 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.

Table 1. The advantages of insulin pump therapy

Similar or better glycemic control with multiple daily injection regimen
Lower frequency of hypoglycemia
Lower fluctuations in blood glucose level change
Continuous flow of short-acting insulin and continuous basal insulin level
Accurate adjustment of basal insulin requirement
Greater lifestyle flexibility
Improvement in quality of life
Higher patient satisfaction

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 (insulin 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

1- Investigation of the eligibility of diabetes mellitus patients for insulin pump therapy	Daily capillary blood glucose monitoring and insulin doses should be recorded on a chart before the start of CSII. Patients should consult with their health care providers and be competent to approach their illness and carbohydrate intake
2- Calculation of total-basal-bolus insulin doses	Total dose: Multiple daily injection dose x0.75 Basal insulin: Total dose x 0.5 (in young patients 0.4)/24 hours in equivalent doses Bolus insulin: Total dose-Basal dose /3 equal doses for each meal
3- Dietary regulation in diabetic patients	Patients should follow a calorie-restricted diet evenly distributed during the day during insulin dosage adjustment. Thus, carbohydrate counting for meal and insulin-to-carbohydrate ratio can be used to determine the total daily insulin requirement
4- Basal insulin dose adjustment	Total basal insulin dose should be divided into equal doses during 24 hours, and adjusted according to fasting glucose level. The morning dose of insulin is increased to control hyperglycemia caused by counter-regulatory hormones
5- Adjustment of basal insulin infusion rates	Conservative glycemic targets should be 70-140 mg/dL before meal, 100-140 mg/dl at night and 90 mg/dL after 3:00 am in the morning. Fasting blood glucose targets in pregnant women should be 60-90 mg/dL, and 100-160 mg/dL in patients without hypoglycemic symptoms. One unit of insulin is given for every 30 mg/dL over target
6- Adjustment of bolus insulin doses	Bolus insulin doses are titrated according to postprandial blood glucse values. At the beginning, bolus insulin is increased by one unit for every 30 mg/dL over target. In this way, insulin dose can be increased until postprandial glucose value is at the desired level
7- Calculation of insulin sensitivity factor (ISF) and insulin-to-carbohydrate ratio (ICR)	When blood glucose regulation is achieved, the insulin sensitivity factor is calculated by dividing total daily dose into 1800, and insulin- to-carbohydrate ratio by dividing into 500. Then the patient is given an education on blood glucose control and carbohydrate counting
8- Patient education in blood glucose control	Bolus insulin dose is calculated by dividing carbohydrate intake as calorie into insulin-to-carbohydrate ratio. Deviation of the blood glucose concentration from the target range is divided into ISF, and added or removed to bolus insulin dose. The patient is given instruction to self-adjust and decrease insulin dose according to daily activity and exercise routines

Figure 1. The modulation of continuous subcutaneous insulin infusion pump therapy

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

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

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.

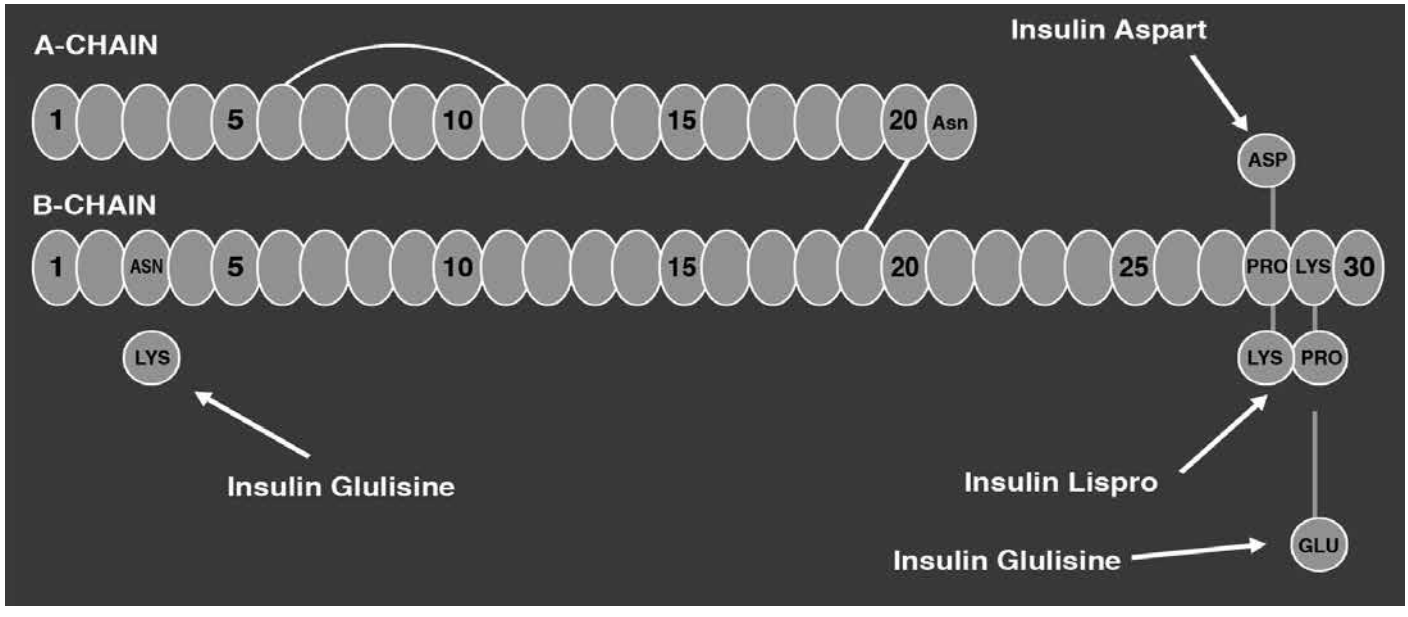

Figure 2. Molecular structure of rapid-acting insulin analogues-aspart, lispro, and glulisine

References

1. King H, Auert RE, Herman WH. Global burden of diabetes, 1995-2025: prevalence, numerical estimates and projections. Diabetes Care 1998;21:1414-1431.
2. Satman I, Omer B, Tutuncu Y, Kalaca S, Gedik S, Dinccag N, Karsidag K, Genc S, Telci A, Canbaz B, Turker F, Yilmaz T, Cakir B, Tuomilehto J; TURDEP-II Study Group. Twelve-year trends in the prevalence and risk factors of diabetes and prediabetes in Turkish adults. Eur J Epidemiol 2013;28:169-180.
3. American Diabetes Association. Standards of medical care. Diabetes Care 2009;32:13-61.
4. Singh SR, Ahmad F, Lal A, Yu C, Bai Z, Bennett H. Efficacy and safety of insulin analogues for the management of diabetes mellitus: a meta-analysis. CMAJ 2009;180:385-397.
5. Hirsch IB. Insulin analogues. N Engl J Med 2005;352:174-183.
6. DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. JAMA 2003;289:2254-2264.
7. Bruttomesso D, Costa S, Baritussio A. Continuous subcutaneous insulin infusion (CSII) 30 years later: still the best option for insulin therapy. Diabetes Metab Res Rev 2009;25:99-111.
8. Morviducci L, Di Flaviani A, Lauria A, Pitocco D, Pozzilli P, Suraci C, Frontoni S; CSII Study Group Of Lazio Region, Italy. Continuous subcutaneous insulin infusion (CSII) in inpatient setting: unmet needs and the proposal of a CSII unit. Diabetes Technol Ther 2011;13:1071-1074.
9. Schmid V, Hohberg C, Borchert M, Forst T, Pfützner A. Pilot study for assessment of optimal frequency for changing catheters in insulin pump therapy-trouble starts on day 3. J Diabetes Sci Technol 2010;4:976-982.
10. Bode BW. Use of rapid-acting insulin analogues in the treatment of patients with type 1 and type 2 diabetes mellitus: insulin pump therapy versus multiple daily injections. Clin Ther 2007;29:135-144.
11. Migdalis IN. Insulin analogs versus human insulin in type 2 diabetes. Diabetes Res Clin Pract 2011;93:102-104.
12. De Leeuw I, Vague P, Selam JL, Skeie S, Lang H, Draeger E, Elte JW. Insulin detemir used in basal-bolus therapy in people with type 1 diabetes is associated with a lower risk of nocturnal hypoglycaemia and less weight gain over 12 months in comparison to NPH insulin. Diabetes Obes Metab 2005;7:73-82.
13. Heise T, Pieber TR. Towards peakless, reproducible and long-acting insulins. An assessment of the basal analogues based on isoglycaemic clamp studies. Diabetes Obes Metab 2007;9:648-659.
14. Mudaliar SR, Lindberg FA, Joyce M, Beerdsen P, Strange P, Lin A, Henry RR. Insulin aspart (B28 asp-insulin): a fast-acting analog of human insulin: absorption kinetics and action profile compared with regular human insulin in healthy nondiabetic subjects. Diabetes Care 1999;22:1501-1506.
15. Rosenfalck AM, Thorsby P, Kjems L, Birkeland K, Dejgaard A, Hanssen KF, Madsbad S. Improved postprandial glycaemic control with insulin aspart in type 2 diabetic patients treated with insulin. Acta Diabetol 2000;37:41-46.
16. Heller SR, Colagiuri S, Vaaler S, Wolffenbuttel BH, Koelendorf K, Friberg HH, Windfeld K, Lindholm A. Hypoglycaemia with insulin aspart: a double-blind, randomised, crossover trial in subjects with Type 1 diabetes. Diabet Med 2004;21:769-775.
17. Bode B, Weinstein R, Bell D, McGill J, Nadeau D, Raskin P, Davidson J, Henry R, Huang WC, Reinhardt RR. Comparison of insulin aspart with buffered regular insulin and insulin lispro in continuous subcutaneous insulin infusion: A randomized study in type 1 diabetes. Diabetes Care 2002;25:439-444.
18. DeVries JH, Snoek FJ, Kostense PJ, Masurel N, Heine RJ; Dutch Insulin Pump Study Group. A randomized trial of continuous subcutaneous insulin infusion and intensive injection therapy in type 1 diabetes for patients with long-standing poor glycemic control. Diabetes Care 2002;25:2074-2080.
19. Raskin P, Bode BW, Marks JB, Hirsch IB, Weinstein RL, McGill JB, Peterson GE, Mudaliar SR, Reinhardt RR. Continuous subcutaneous insulin infusion and multiple daily injection therapy are equally effective in type 2 diabetes: a randomized, parallel-group, 24-week study. Diabetes Care 2003;26:2598-2603.
20. EQuality1 Study Group--Evaluation of QUALITY of Life and Costs in Diabetes Type 1, Nicolucci A, Maione A, Franciosi M, Amoretti R, Busetto E, Capani F, Bruttomesso D, Di Bartolo P, Girelli A, Leonetti F, Morviducci L, Ponzi P, Vitacolonna E. Quality of life and treatment satisfaction in adults with Type 1 diabetes: a comparison between continuous subcutaneous insulin infusion and multiple daily injections. Diabet Med 2008;25:213-220.
21. St Charles ME, Sadri H, Minshall ME, Tunis SL. Health economic comparison between continuous subcutaneous insulin infusion and multiple daily injections of insulin for the treatment of adult type 1 diabetes in Canada. Clin Ther 2009;31:657-667.
22. Hirsch IB, Bode BW, Garg S, Lane WS, Sussman A, Hu P, Santiago OM, Kolaczynski JW; Insulin Aspart CSII/MDI Comparison Study Group. Continuous subcutaneous insulin infusion (CSII) of insulin aspart versus multiple daily injection of insulin aspart/insulin glargine in type 1 diabetic patients previously treated with CSII. Diabetes Care 2005;28:533-538.
23. Monami M, Lamanna C, Marchionni N, Mannucci E. Continuous subcutaneous insulin infusion versus multiple daily insulin injections in type 1 diabetes: a meta-analysis. Acta Diabetol 2010;47:77-81.
24. Bragd J, von Döbeln A, Lins PE, Adamson U, Bergström J, Oskarsson P. Basal insulin substitution with glargine or continuous subcutaneous insulin infusion in adult type 1 diabetes patients-a randomized controlled trial. Diabetes Technol Ther 2010;12:689-693.
25. Cander S, Kiyici S, Deligonul A, Oz Gul O, Unal OK, Sakallı M, Tuncel E, Imamoglu S. Treatment Efficacy of Subcutaneous Insulin Infusion Therapy in Type1 Diabetic Patients. Turk J Endocrinol Metab 2010;14:80-84.
26. Pankowska E, Blazik M, Dziechciarz P, Szypowska A, Szajewska H. Continuous subcutaneous insulin infusion vs. multiple daily injections in children with type 1 diabetes: a systematic review and meta-analysis of randomized control trials. Pediatr Diabetes 2009;10:52-58.
27. Pickup JC, Sutton AJ. Severe hypoglycaemia and glycaemic control in Type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion. Diabet Med 2008;25:765-774.
28. Pickup JC, Renard E. Long-acting insulin analogs versus insulin pump therapy for the treatment of type 1 and type 2 diabetes. Diabetes Care 2008;31:140-145.
29. Reznik Y, Morera J, Rod A, Coffin C, Rousseau E, Lireux B, Joubert M. Efficacy of continuous subcutaneous insulin infusion in type 2 diabetes mellitus: a survey on a cohort of 102 patients with prolonged follow-up. Diabetes Technol Ther 2010;12:931-936.
30. Johnson SL, McEwen LN, Newton CA, Martin CL, Raskin P, Halter JB, Herman WH. The impact of continuous subcutaneous insulin infusion and multiple daily injections of insulin on glucose variability in older adults with type 2 diabetes. J Diabetes Complications 2011;25:211-215.
31. Herman WH, Ilag LL, Johnson SL, Martin CL, Sinding J, Al Harthi A, Plunkett CD, LaPorte FB, Burke R, Brown MB, Halter JB, Raskin P. A clinical trial of continuous subcutaneous insulin infusion versus multiple daily injections in older adults with type 2 diabetes. Diabetes Care 2005;28:1568-1573.
32. Monami M, Lamanna C, Marchionni N, Mannucci E. Continuous subcutaneous insulin infusion versus multiple daily insulin injections in type 2 diabetes: a meta-analysis. Exp Clin Endocrinol Diabetes 2009;117:220-222.
33. Vajo Z, Fawcett J, Duckworth WC. Recombinant DNA technology in the treatment of diabetes: insulin analogs. Endocr Rev 2001;22:706-717.
34. Hartman I. Insulin analogs: impact on treatment success, satisfaction, quality of life, and adherence. Clin Med Res 2008;6:54-67.
35. Hedman CA, Lindstrom T, Arnqvist HJ. Direct comparison of insulin lispro and aspart shows small differences in plasma insulin profiles after subcutaneous injection in type 1 diabetes. Diabetes Care 2001;24:1120-1121.
36. Homko C, Deluzio A, Jimenez C, Kolaczynski JW, Boden G. Comparison of insulin aspart and lispro: pharmacokinetic and metabolic effects. Diabetes Care 2003;26:2027-2031.
37. Plank J, Wutte A, Brunner G, Siebenhofer A, Semlitsch B, Sommer R, Hirschberger S, Pieber TR. A direct comparison of insulin aspart and insulin lispro in patients with type 1 diabetes. Diabetes Care 2002;25:2053-2057.
38. Li YB, Liu J, Liao ZH, Liao Y, Deng WP, Weng JP. The comparison of insulin aspart and human soluble insulin used in continuous subcutaneous insulin infusion in newly diagnosed type 2 diabetic patients. Zhonghua Yi Xue Za Zhi 2005;85:2472-2476.
39. Siegmund T, Amelunxen SV, Kaiser M, Schumm-Draeger PM. Pump compatibility of insulin aspart compared to insulin lispro with respect to catheter complications and dermal/subcutaneous irritations in patients (P) with type 1 diabetes (T1D) undergoing continuous subcutaneous insulin infusion (CSII) therapy. Diabetes 2005;54(Suppl 1):A105.
40. Bode BW. Comparison of pharmacokinetic properties, physicochemical stability, and pump compatibility of 3 rapid-acting insulin analogues-aspart, lispro, and glulisine. Endocr Pract 2011;17:271-280.
41. Van Bon AC, Bode BW, Sert-Langeron C, DeVries JH, Charpentier G. Insulin glulisine compared to insulin aspart and to insulin lispro administered by continuous subcutaneous insulin infusion in patients with type 1 diabetes: a randomized controlled trial. Diabetes Technol Ther 2011;13:607-614.
42. Bartolo PD, Pellicano F, Scaramuzza A, Sardu C, Casetti T, Bosi E, Miselli V, Brandolini S, Fabbri T, Meandri P, Cannata F. Better postprandial glucose stability during continuous subcutaneous infusion with insulin aspart compared with insulin lispro in patients with type 1 diabetes. Diabetes Technol Ther 2008;10:495-498.