Insulin Lispro - A Review

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Introduction

The ultimate goal of insulin treatment is to provide physiological replacement of insulin. Although it has been often considered as an elusive goal[1] the introduction of new insulin analogs may be one of the steps that will bring us closer to this goal.

Subcutaneous administration of short acting insul in before the meal should control postprandial increase in blood glucose levels. With currently available short acting insulin (regular, soluble), however, appropriate insulin response to the meal cannot be mimicked successfully. The main reason for the failure is slow absorption of regular insulin. Regular insulin exists as hexamers (clusters of 6 insulin molecules) in solution as well as in subcutaneous tissue. It can be absorbed into blood vessels only after dissociation into diamers amid monomers. This prolonged absorption results in a delayed, blunted peak and longer duration of action of regular insulin when compared to the pattern of physiological insulin secretion. For the patient it means-higher postprandial blood glucose and increased risk for late postprandial hypoglycemia. More than ten) ears ago it was recognized that certain changes in the insulin molecule could increase the rate of insulin absorption.

Insulin Lispro: Molecule and Pharmacokinetics

The first monometric insulin analog to be approved for marketing in the USA and European Union was insulin lispro. It is obtained by the reversal of two amino acids (lysine and proline) in the sequence of the C terminal end of the B chain of the insulin molecule. The same sequence of amino acids exists in the natural nioleucle of IGF-1, that is very similar to insulin but with a lower tendency to self associate[2]. Although insulin lispro forms discrete hexanicres in solution they dissociate more rapidly into monomers following subcutaneous injecion (Figure I).

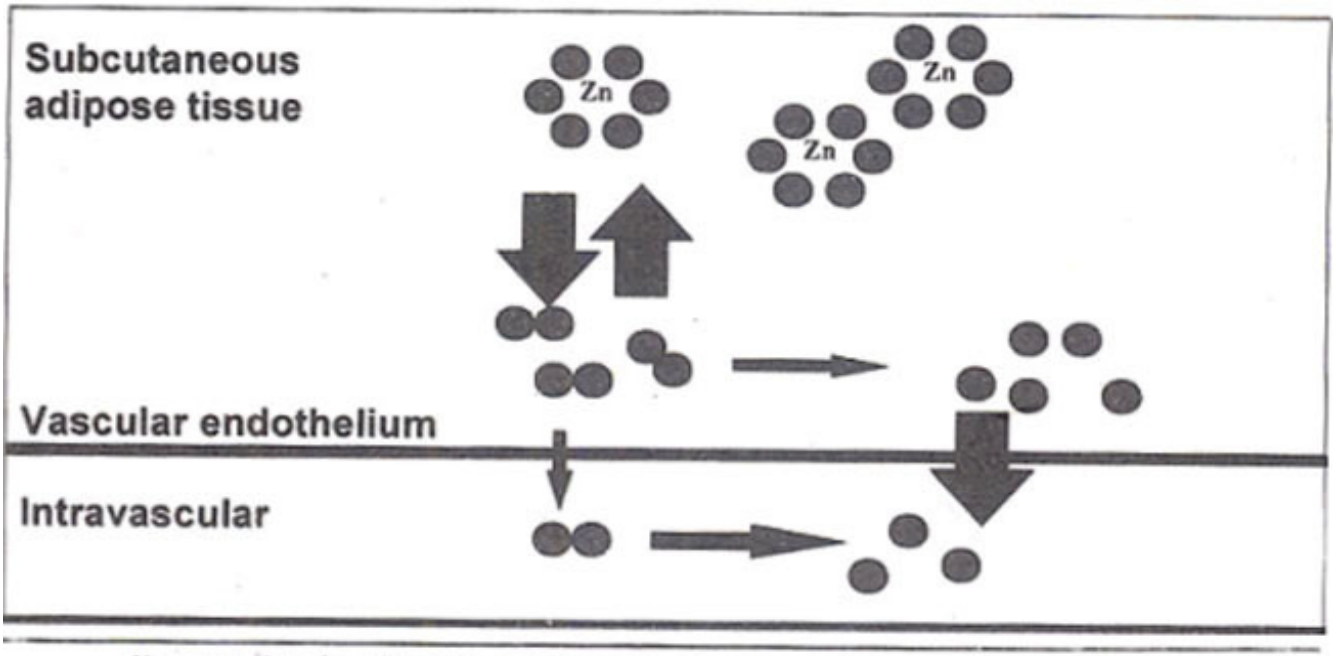

Figure 1. Insulin absorption during subcutaneous injection of human insulin

Animal studies have demonstrated that insulin lispro has neither mutagenic nor carcinogenic potential[3]. Pharmacokinetic and glucodynamic studies in normal human volunteers have confirmed the favourable Lime action profile of insulin lispro. The onset of action is 0-15 minutes, peak blood levels are achieved after 20-60 minutes and the duration of action is 4-5 hours (Figure 2).

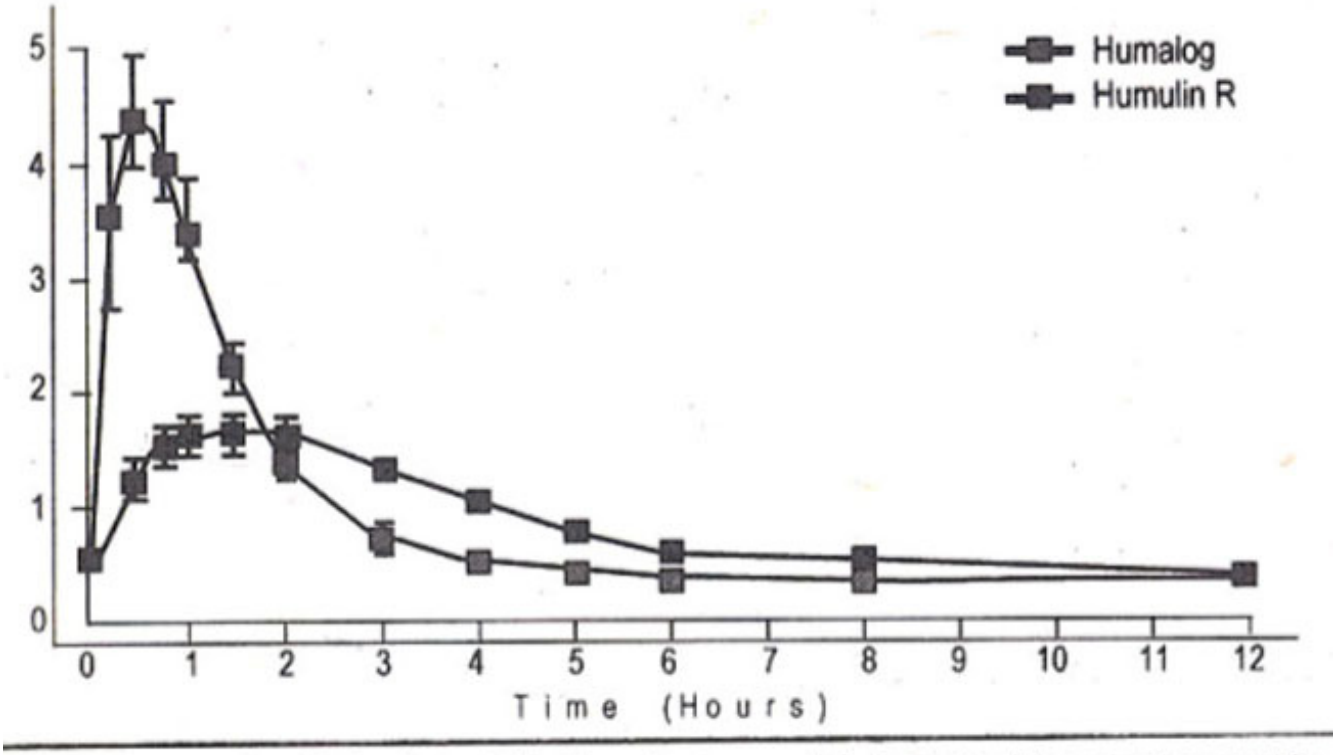

Figure 2 Serum Insulin levels (ng/ml) after subcutaneous injecion in healthy volunteers (n=10).

Compared to regular insulin, insulin lispro achieved peak concentrations that were two times higher in less than half the time[4]. The potency of both types of insulin was similar. asseenby the equal area under the curve. These differences were preserved for the different doses[5] and the different injection sites[6]. A positive feature of insulin lispro is that the time 1.0 peak positive feature of insulin lispro is that the time 1.0 peak activity and duration of action remain the same over a wide dose range. Increased doses of regular human insulin produced delay in peak activity and prolongation in duration of action.

Acute effect of lispro insulin: Better postprandial blood glucose control

Improvement in postprandial glucose control is an expected and well established effect of insulin n lispro This has been well demonstrated in various groups of patients and with different kind of meals. Pampaneli and co-workers[6] studied 6 patients with Type 1 diabetes mellitus of short duration with residual beta cell function. Insulin lispro, when given immediately before the meal (mixed meal of 692 Kcal) to these patients, resulted in greater decreases of post meal hyperglycemia as compared with regular insulin. This difference was more relevant when the regular insulin was given immediately before the meal, but was still present when regular insulin was given 30 minutes before the meal. Plasma insulin levels were measured with each instilin regiment and in a group of non-diabetic volunteers. After injection of insulin lispro plasma insulin peaked earlierand was superimposable on that of non-diabetic subjects. Insulin lispro appeared to be a more convenient. efficient and safe insulin preparation than regular insulin for the in patients with short duration of Type I diabetes and residual fucniion of beta cell.

The same group of investigators demonstrated that in Type 1 diabetes patients without residual insulin secretion, insulin lispro provided better postprandial blood glucose control compared to regular insulin

within the first three hours[8]. After three hours there was rapid increase in blood glucose levels in patient who received insulin lispro, while those treated with regular insulin had a much slower increase in blood glucose values in the period 3-6 hours after the injection.

Due to the vezy rapid onset of action insulin lispro could possibly be injected after the meal, Schernthaner and colleagues[9] compared postpraiidial blood glucose control of 16 Type I diabetes patients administerating short acting insulin at 5 different time points. The first time point was insulin lispro given immediately before the meal, the second was insL tin lispro 15 minutes after the beginning of the meal, the third was regular insulin immediately before the meal, the fourth was reguLar insulin 20 minutes before the meal and the fifth was regular insulin 40 minutes before the meal. The best posiprandial blood glucose control was achieved when insulin lispro was given immediately before the meal. Regular insulin given 20 minutes before the meal appeared to be better than regular insulin given immediately before the meal. Insulin lispro given after the meal had a similar glucodynamic effccL to regular insulin given 0 or 20 minutes before the meal.

The most obvious improvement in postprandial blood glucose control was achieved with a carbohydrate rich meal[10]. Ten patients with Type 1 diabetes and vcty good metabolic control were tested in a double blind randomized trial comparing 8 hour postprandial blood glucose excursion after the administration of regular insulin with insulin lispro. Both types of insulin were given immediately before a meal of pizza, coca and tiramisu. Higher and longer lasting blood glucose values were recorded after the administration of regular insulin, whereas with the administration of insulin hspro blood glucose values achieved short lasting peak by the end of the first hour (Figure 3).

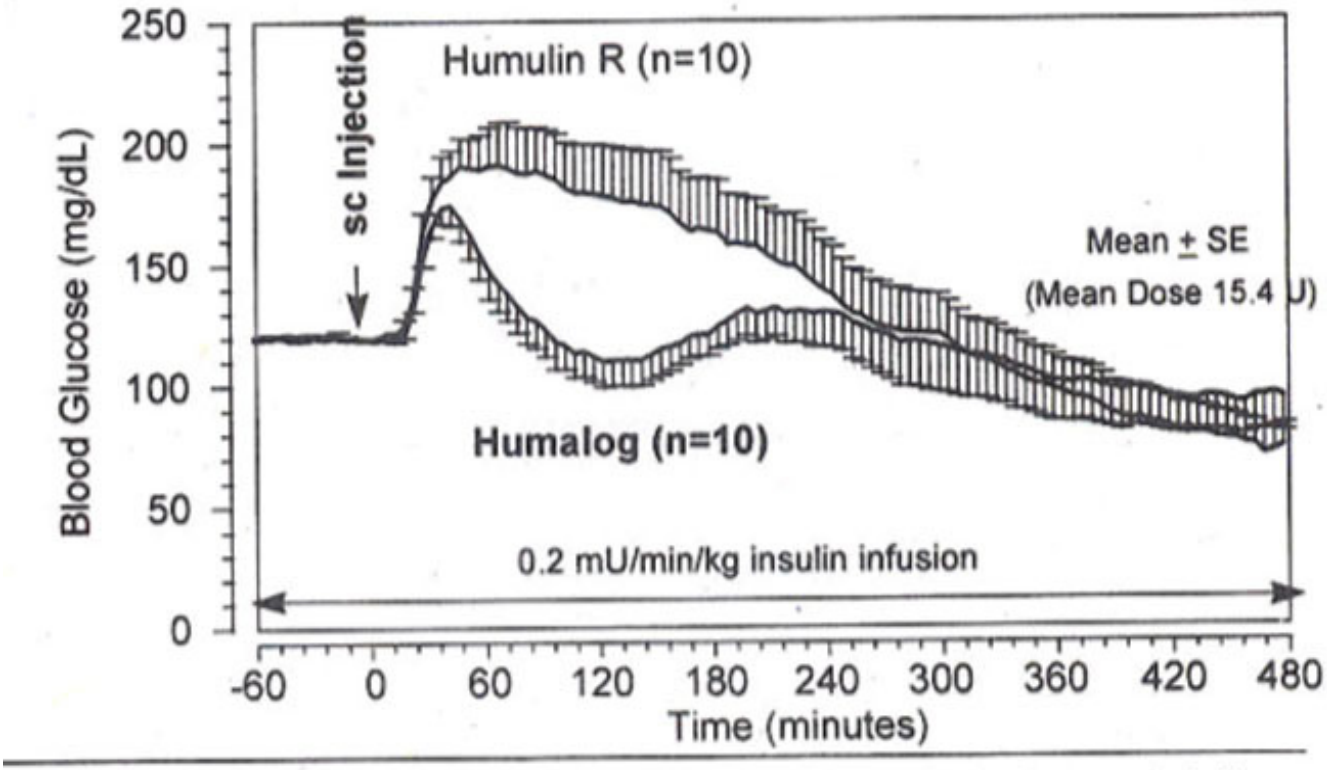

Figure 3. Blood glucose measurements in type 1 patients following high caloric meal challenge

Long term use of insulin hspro

Insulin lispro has been most extensively tested in Type I diabetes patients using intensive insulin treatment. A cross-over study with 1037 patients compared insulin lispro with human regular insulin[11]. Insulin lispro was given immediately before each meal, whereas regular insulin was given 30 minutes

before the meals. NPH insulin was used once or twice daily as a basal insulin in both treaLment periods lasting three months. Improvement in one and two hour posiprandial blood glucose and reducation in the number of hypoglycemic episodes was found in insulin lispro treatment period (Figure 4).

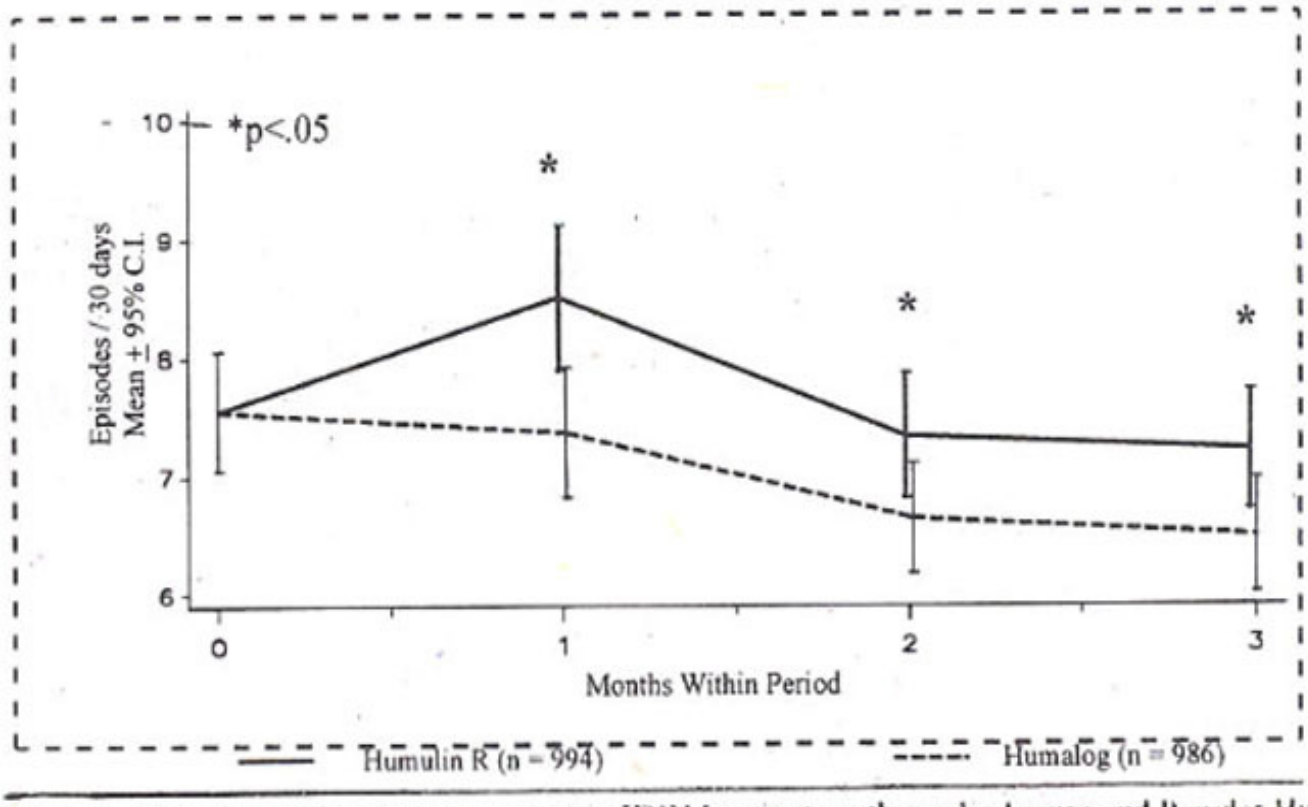

Figure 4 Hypoglycaemic rate (non severe) in IDDM patients with insulin Lispro and Regular Human Insulin

The nuthbcr'öf hypoglycemic episodes during the night was also lower during the insulin lispro titatment period.

There were no differences in the level of Hb A ic as well as in the proportion of short acting to long acting insulin between the two treatment periods. The finding of improved posiprandial blood glucose levels without change in HbA Ic may lead to the conclusion that there is deterioration in blood glucose levels in post absorptive period, if this is correct, the improvement in overall glycernic control might be achieved only when the optimal dose of basal insulin is used. This hypothesis was examined by Torlonc and co-workers[8]. The effect of insulin lispro, regular insulin, insulin lispro with NPH and regular insulin with NPH on 6 hour postprandial glucose control in 10 patients with Type 1 diabetes mellitus as examined, The study demonstrated that when insulin lispro was used adequately with basal insulin it can improve not only early, but also late plasma glucose concentrations, as compared with regular insulin. These observations led to the conclusion that NPH insulin should be given with insulin lispro whenever the interval between insulin injection is greater than 34 hours. More studies are needed to elucidate the effect of the tong term treatment with optimal combination of insulin lispro and basal insulin on the level of HbAic.

The use of insulin lispro in exercising diabetes patients was examined by Tuominen[12]. Compared to regular insulin, insulin lispro increased the risk of exercise induced hypoglycemia whenever the exercise was performed shortly after the insulin injection (40 minutes). the risk of exercise induced hypoglycemia was decreased. whenever, the exercise was perfonned later after the insulin injcction and the meal (180 minutes). As exercise is usually not performed until 2-3 hours after the Incal, insulin lispro would be the better choice for active patients with type 1 diabetes mellitus.

Quality of life aspects

In the Benelux countries in 110 patients' quality of life questionnaires were evaluated while using regular insulin and insulin lispro each for 3 months. This study evaluated the patients perception of insulin lispro in a three months study period[13]. Thirty five percent of the patients felt they had better control of their glycernia, whereas, 53% reported no change and 13% worse control Thirty-six percent of the patients had fewer hypoglycemia with insulin Iispm, while 40 reported no change and 24% had an increase in episodes. The most frequently reported positive features of insulin lispro were the ability to eat immediately after injection, more freedom and feeling better. Treatment satisfaction was demonstrated by 80% of the patients electing to continue intensive therapy with insulin lispro after the completion of the study.

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