

Short-acting insulin analogues: Are they better than regular insulin for people with type 2 diabetes?



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Nowadays people with insulin-dependent diabetes have a choice between various types of insulin. Some people still use porcine insulin, manufactured from pig extracts. However, most people use genetically engineered “human” insulin. Insulin analogues, which have been available since the mid 1990s, are a further option. You can read more about insulin and diabetes here (URL: <http://www.gesundheitsinformation.de/diabetes-insulin-therapy.3321561.html>).

Insulin analogues are manufactured by changing the basic structure of the insulin molecule. These changes mainly affect how long it takes for the insulin to start lowering the blood sugar levels and how long it works for.

In terms of how long they work for, insulin products can be grouped into three main categories: short- (or rapid-) acting, intermediate-acting and long-acting insulin. Short-acting insulin, also known as “mealtime” or “bolus” insulin, counteracts the blood sugar increase that follows meals. Intermediate-acting and long-acting insulin, also known as “basal insulin”, covers the basic insulin needs throughout the day.

Three types of short-acting insulin analogues are currently available in Germany: insulin lispro (“Humalog” and “Liprolog”), insulin aspart (“NovoRapid”) and insulin glulisine (“Apidra”). These work faster and over a somewhat shorter time period than regular human insulin.

Together with researchers from the University of Graz in Austria, researchers at the German Institute for Quality and Efficiency in Health Care (IQWiG) studied whether short-acting insulin analogues have health-related advantages over regular short-acting human insulin for people with diabetes. Because the treatment approach is very different for people with type 1 and type 2 diabetes, the researchers first focused on treatment for people with type 2 diabetes.

Different types of insulin

One clear aim of insulin therapy is the prevention of complications arising from poorly controlled blood sugar levels. Successful therapy should also prevent blood sugar

fluctuations that lead to low blood sugar (hypoglycaemia) or high blood sugar (hyperglycaemia). From the patients’ point of view, a treatment which makes everyday life easier would be a further advantage.

It is important to differentiate between type 1 and type 2 diabetes: People who have type 1 diabetes do not produce insulin themselves. Compared to people who have type 2 diabetes, it is more common for them to experience relatively strong blood sugar fluctuations during insulin therapy.

People who have type 2 diabetes usually still produce insulin but it does not work well enough anymore. They are “insulin-resistant”. Big blood sugar fluctuations with dangerously low or high blood sugar levels are therefore far less common in people who have type 2 diabetes.

There is such a big difference between the two different types of diabetes that a certain medication could have a completely different effect in someone with type 1 diabetes than it does in someone with type 2 diabetes. That is why a new type of insulin has to be tested in both patient groups if it is to be used in both groups.

Evaluation of insulin

If an insulin analogue has obvious advantages compared to regular human insulin, this ought to be easy to prove in well-designed scientific studies. To do this, a clinical trial involving people with diabetes should be carried out over a long period of time, following the standard approach used in many areas of medicine. First, volunteers are recruited for a clinical trial. They are then randomly assigned to, for example, two different groups (this is called randomisation). This provides the best guarantee that the two groups do not differ in terms of, for instance, severity of illness. The people in one group then use regular human insulin and those in the other group get an insulin analogue. Because the randomisation made sure that the two treatment groups were very similar before receiving treatment, any differences in treatment outcome are likely to be due to the treatment received rather than other factors.

For this reason IQWiG focused on methodically reliable scientific trials like this in their research. However, the search was not as fruitful as hoped: although the researchers found a lot of publications about treatment with insulin analogues in scientific journals, only a

handful of these involved a direct comparison with regular human insulin under comparable conditions over several months. To be certain that they had not left out any important information, the IQWiG researchers also asked the manufacturers of insulin analogues for any previously unpublished information.

Two trials involving a total of 1,800 participants compared insulin glulisine with regular human insulin. There were five comparative trials on insulin lispro, with 860 participants in total. Although they did find one trial on insulin aspart, the data had only been partly published. The manufacturer of insulin aspart was not prepared to provide IQWiG with the rest of the data.

What they found

The trials in the analysis were not carried out in a way that made it possible to make a direct and detailed comparison between the two types of insulin. For instance, the clinical trials were not long enough to be able to determine the effects of insulin analogues on the development of complications associated with diabetes, such as eye and kidney damage. So it is still not clear whether one type of insulin is better than the other.

What is more, the insulin was not given to the patients in neutral packaging, so both the patients and doctors participating in the trials knew who was being treated with what. Finally, the people who received regular human insulin were asked to keep a fixed time interval (for example, 30 to 45 minutes) between taking the insulin and eating, which does not necessarily reflect real life use.

The so-called HbA1c level in blood provides a measure of the average blood sugar concentration over the previous three months. It therefore reflects the efficacy of the treatment. High HbA1c levels over long periods of time indicate a higher risk of complications associated with diabetes. The researchers found that there was no significant difference between the HbA1c levels of patients who were treated with insulin analogues and those who received regular human insulin.

One important factor for patients is how regularly they have (severe) high or low blood sugar. There was no difference between the two types of insulin in this respect. The same is true for the frequency of low blood sugar levels at night (nocturnal hypoglycaemia). IQWiG therefore came to the overall conclusion that the currently available good-quality trials do not show that, compared to regular

human insulin, insulin analogues offer an additional health benefit for people with type 2 diabetes.

Several trials also compared the participants' treatment satisfaction and perceived quality of life. Again, the results did not show any significant differences between the different types of insulin.

Other adverse effects

Another important aspect for people with diabetes is weight gain. The available trials also revealed no difference here. Participants who used short-acting insulin analogues gained just as much weight during the trial as those who used regular human insulin (about two to five kilos on average).

Because the trials only lasted a few months, no conclusions can be drawn about the long-term safety of insulin analogues. Regulatory authorities also consider this to be an important issue. One concern is that modifying the natural structure of insulin could lead to a change in the body's hormonal balance, and that using modified insulin over longer periods of time could have undesirable effects. Long-term monitoring of patients should help to clarify these issues.

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Note

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Sources

German Institute for Quality and Efficiency in Health Care (IQWiG). *Rapid-acting insulin analogues for the treatment of diabetes mellitus type 2. Final report A05-04. Version 1.0.* Cologne: IQWiG. December 2005. [Executive summary (URL: http://www.iqwig.de/download/A05-04_Executive_summary_Rapid-acting_insulin_analogues_for_the_treatment_of_diabetes_mellitu)] [Full text (URL: http://www.informedhealthonline.org/http://www.iqwig.de/download/A05-04_Final_Report_Rapid-acting_insulin_analogues_for_the_treatment_of_diabetes_mellitus_type_)]

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