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Type 2 diabetes: Are long-acting insulin analogues better than regular long-acting human insulin?

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IQWiG

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People who have type 2 diabetes no longer produce enough insulin, or the insulin in their bodies does not work properly (they are "insulin-resistant"). Insulin is needed to transport the sugar in our blood, which comes from foods and drinks, into the cells of our body. Here the sugar is converted into energy. If you do not have enough insulin, the sugar in your blood cannot be used properly and you have high blood sugar levels.

Many people who have type 2 diabetes are able to control their blood sugar without using medication by doing more exercise and losing some weight. If that is not enough to make a difference, tablets that help to reduce blood sugar levels (so-called oral diabetes medication) can be used. Some people with type 2 diabetes need insulin too.

People who have type 1 diabetes always need insulin shots: their pancreas only produces very little insulin or none at all, so they have to inject the insulin their body needs. This research summary is about type 2 diabetes only.

Different kinds of insulin

People who have diabetes and need insulin therapy now have a choice of different kinds of insulin. Up until the mid 1980s, insulin was taken from the pancreas of pigs and cattle. After that, artificially produced insulin, so-called human insulin, became more commonly used. Human insulin is chemically identical to the insulin that humans produce naturally. In many countries, including Germany, animal insulin is no longer used much. Most people use human insulin nowadays. There is also another kind of insulin, the so-called insulin analogues. Several insulin analogues have been licensed for treatment since the mid 1990s.

Insulin analogues are produced artificially too, but their chemical structure is modified. The main aim of modifying their structure is to influence how long it takes for them to start lowering blood sugar levels and how long the effect lasts.

Insulin products can be grouped into three main categories according to how long they work for: short-acting (or rapid-acting), intermediate-acting and long-acting insulin. Short-acting insulin is used to lower blood sugar levels relatively quickly, for example just before mealtimes. Intermediate-acting and long-acting insulin, also known as "basal insulin", cover the basic insulin needs throughout the day.

Two kinds of long-acting insulin analogues are currently available in Germany, called insulin glargine (brand name: "Lantus") and insulin detemir (brand name: "Levemir"). They are meant to have a longer and more steady effect than long-acting human insulin and, like human insulin, can be used in combination with oral diabetes medication.

Research on long-acting insulin analogues

The German Federal Joint Committee (G-BA) commissioned the German Institute for Quality and Efficiency in Health Care (IQWiG) – the publisher of this website – to look at whether patients with diabetes can benefit from long-term therapy with long-acting insulin analogues. 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. They worked on this together with researchers from the University of Graz.

The researchers wanted to know whether long-acting insulin analogues had advantages for patients compared to long-acting human insulin. They were also interested in how insulin glargine and insulin detemir compared to each other. To find answers, they looked at the benefits and adverse effects that each of the medications had.

In their search for studies, they only looked for randomised controlled trials. This kind of study involves randomly assigning the participants to different groups. One of the groups uses one kind of long-acting insulin analogue, and the other group or groups use long-acting human insulin or another kind of insulin analogue. Doing studies in this way helps to ensure that any differences between the groups are due to the insulin being tested. The researchers were only interested in trials which lasted at least 24 weeks.

The researchers searched medical databases for trials like these, and they also asked the manufacturers of the medications if there had been any other trials. A total of 18 trials were found, 13 of which had already been published. The other 5 trials had not yet been published,

but the manufacturers gave the researchers the data they had. Of the 18 trials, 15 compared a long-acting insulin analogue with NPH insulin (delayed-action insulin based on human insulin). Insulin glargine was tested in 9 of the trials and insulin detemir was tested in 6 trials. The other 3 trials directly compared the two insulin analogues with each other. The trials involved about 8,000 participants who were between 55 and 62 years old on average.

In 11 of the trials, the insulin was used as well as oral diabetes medication, and in 6 trials it was used in intensive insulin therapy. In intensive insulin therapy, people eat whatever amount of food they want, when they want, and regularly adapt the amount of insulin they inject according to how much they need. One trial looked at different treatment regimens. There was only one long-term trial that lasted five years. The rest of the trials only lasted between 6 and 12 months.

In 7 out of the 9 trials that compared insulin glargine with NPH insulin, the NPH insulin was not used in the way that it is generally used in practice in Germany: the participants only injected it once a day. It is usually injected more often in everyday life. This means that the results of this trial cannot be directly applied to German patients.

Long-term advantages and disadvantages of long-acting insulin analogues

The researchers were particularly interested in whether, compared to human insulin, long-acting insulin analogues could be better at preventing serious complications of type 2 diabetes, such as cardiovascular disease (heart and circulation problems), visual loss, kidney problems or the need for amputations. Unfortunately, however, the trials hardly provided any data on this. The five-year trial did not show any differences between insulin glargine and NPH insulin in terms of heart problems. Because complications usually only arise after years or even decades, most of the trials were too short to be able to answer these questions.

The five-year trial looked at the frequency of problems affecting the inner lining of the back of the eye in people who were taking insulin glargine or NPH insulin. These eye problems arise if the high levels of sugar in the blood damage the small blood vessels in the eye over time. The researchers concluded that, in this trial, there was no suggestion of harm from insulin glargine.

Short-term advantages and disadvantages of long-acting insulin analogues

The researchers also looked at data on the people's HbA1c levels. This is a value which can be measured in blood tests. It gives you an indication of how high your blood sugar has been on average over the last three months. In nearly all of the trials, treatment was considered to be a success if a person's HbA1c levels had decreased by the end of the trial.

One good outcome of treatment for people with type 2 diabetes would be if they had fewer episodes of low blood sugar (hypoglycaemia). Hypoglycaemia is when blood sugar drops to a dangerously low level, which can cause shaking, confusion as well as cramps and loss of consciousness. Low blood sugar can be an adverse effect of insulin therapy.

Taking these factors into consideration, the researchers could not find any proof that long-acting insulin analogues have any overall advantages over regular insulin. They only found some evidence which indicated that insulin detemir may cause fewer episodes of low blood sugar than NPH insulin does. But this was only true for people who used it as basal insulin one or two times a day in addition to taking oral diabetes medication. The results of the long-term trial suggested that people who used insulin glargine had fewer serious episodes of low blood sugar than those who used NPH insulin.

The trials that compared the two different insulin analogues with each other did not show that one had any advantages over the other either. But, compared to the people who were using insulin glargine, more people who were using detemir dropped out of the trials due to adverse effects such as allergic skin reactions or inflammations at the site of injection.

People who used insulin detemir put on less weight than those who used insulin glargine or NPH insulin, but the difference was not big. Because the trials only lasted a year at most, it is not known whether this is a long-lasting effect.

The IQWiG researchers concluded that the long-term harms and benefits have not been studied enough. People who have diabetes use insulin for years, if not decades. Complications like cardiovascular problems often only arise after many years and it is not known how insulin analogues may affect the likelihood of developing these conditions. It is also too soon to say what effects artificially modifying the structure of insulin may have on the body over time.

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Recent research has suggested that one of these artificial kinds of insulin (insulin glargine) might speed up the development of cancer. Further data needs to be analysed to be more sure though. People who have diabetes and use glargine have many other options, including human insulin. You can read more about that here (URL: http://www.iqwig.de/index.879.en.html) .

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Note

This health information is a summary of a scientific report published by IQWiG. It is not an assessment of the right to have health care services reimbursed by statutory health insurance funds in Germany. By law, decisions about the reimbursement of diagnostic and therapeutic procedures can only be made by the German Federal Joint Committee (G-BA). The Federal Joint Committee takes IQWiG reports into consideration in its decision-making process. You can find information about the decisions of the German Federal Joint Committee on its English-language website, www.english.g-ba.de (URL: http://www.english.g-ba.de/) .

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Glossary

evidence

Evidence is what we call scientific proof from well-conducted, good-quality scientific trials that have been carefully designed to answer specific questions. Depending on the types of questions, different scientific research methods (types of study) are most appropriate to find reliable answers to these questions. Randomized controlled trials (RCTs), for example, are the best way to get reliable evidence on the effectiveness of medical treatments (interventions). This type of study, however, is not the best form of evidence for all possible questions, and does not provide the best answers to all kinds of questions, either. Epidemiological studies, for example, are very suitable for establishing well-founded proof for the spreading of a disease in the population.

pancreas

The pancreas is 12 to 18 cm long and lies in a horizontal position in the upper abdomen below the stomach. It produces a digestive juice with digestive enzymes in it, which is released into a duct inside the pancreas. This duct then leads into the intestine. There the enzymes help to break down fat, for example. The pancreas also contains the islets of Langerhans with different cells that produce hormones for the metabolism. Unlike the enzymes, the hormones are not released into the intestine, but into the blood. Alpha cells produce Glucagon, beta cells produce insulin and delta cells somatostatin. These are the three most important hormones for regulating glucose metabolism.

Sources

German Institute for Quality and Efficiency in Health Care (IQWiG). *Long-acting insulin analogues in the treatment of diabetes mellitus type 2. Final report A05-03.* Version 1.1. Cologne: IQWiG. February 2009. [Executive summary (URL: http://www.iqwig.de/download/A05-03_Executive_summary_Long_acting_insulin_analogues_in_the_treatment_of_diabetes_mellitus_] [Full text – in German (URL: http://www.iqwig.de/download/A05-03_Abschlussbericht_Langwirksame_Insulinanaloga_bei_Diabetes_mellitus_Typ_2_V1.1.html)]

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The German Institute for Quality and Efficiency in Health Care (IQWiG)

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Evidence basis of our health information

Our information is based primarily on systematic reviews of the effects of health care. Systematic reviews are necessary to gain an objective picture of health care. In order to do this, a clear question is formulated. Researchers then find all the relevant studies that could answer this question. They then evaluate those studies.

You can find a list of the evidence and other scientific literature on which this information is based at **www.informedhealthonline.org**

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This information was prepared and published by the German Institute for Quality and Efficiency in Health Care (IQWiG). It is based on the evidence and other scientific literature available at the time of publication. The information is intended for the use of patients in Germany. It is not intended to for use to diagnose illnesses and the information is not intended to substitute for medical advice.

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