

# Genetic Engineering in Diabetes

by Cansel Onat and David Rothen

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## Preface

The topic originally stemmed from our common family history. On both of our families we have relatives who are affected by diabetes in some way. Through this common thread of ours we decided on choosing this topic. In this paper we have included various concepts, effects and implications of Insulin. We wanted to find out about its role on the human body and its effects on it, or even what insulin really is and dig deeper. The aim of this paper was to familiarize the students with the implementation of the knowledge on diabetes and find the most efficient way to treat it. Because since each person is different and therefore needs a different treatment to reach overall high adherence. In the process of this paper we helped us to enhance our knowledge regarding those who have to deal with this condition. Through this report we came to know about the importance of insulin and its role on those who are affected by diabetes type 1 and 2.

## Introduction

Insulin, as a medication, is used to cure diabetes, which is a metabolic disease. In the natural metabolism, the body's own hormone "insulin" is needed to absorb glucose into the body's cells. The sugar present in the food can thus be converted into vital energy. When normal exchange stops working, glucose stays in the blood and constantly raises blood sugar levels. In healthy people, the hormone insulin in the pancreas works like a key that unlocks the body's cells for the sugar. When the body is not able to digest glucose due to the fact of the absence of insulin then this person has the metabolic disease, diabetes. This could occur because of inheritance or through a bad eating habit. Therefore there are two different types of diabetes: type 1 diabetes and type 2 diabetes. ([https://de.wikipedia.org/wiki/Diabetes\\_mellitus](https://de.wikipedia.org/wiki/Diabetes_mellitus))

### Type 1 Diabetes

Type 1 diabetes is relatively rare. Less than one-tenth of diabetes diagnoses account for this form. It usually begins in childhood, adolescence or early adulthood.

Type 1 diabetes is an autoimmune disease, where the immune system is directed against the body's own cells. In type 1 diabetes, these are the insulin-producing beta cells of the pancreas, which are completely destroyed in the long term. As a result, the body can no longer produce insulin and there is an absolute insulin deficiency. Thus insulin must be added to the body from the outside.

### Type 2 diabetes

This form of diabetes is by far the most prevalent and increasing worldwide. Type 2

diabetes used to appear mainly in middle to old age. For this reason it is popularly referred to as "adult-onset diabetes". Unfortunately, more and more young people and even children are now suffering from type 2 diabetes.

Most patients with diabetes arise as a result of the so-called "metabolic syndrome", which is characterized by obesity, high blood pressure and a lipid metabolism disorder with elevated blood lipid levels. Type 2 diabetes is a chronic metabolic disease in which the blood sugar level is elevated. The reason for this is insulin resistance. In this case the body cells respond worse to insulin. The hormone actually has the task of transferring the sugar molecules from the blood into the cells. In the case of insulin resistance, this is only insufficiently successful - the sugar accumulates in the blood vessels, what can be a major health risk.

Above all overweight and lack of exercise are factors, that promote insulin resistance, but genetic predisposition also plays a role.

For this reason, the therapy of type 2 diabetes aims both to improve the insulin action on the cells (reduction of insulin resistance), as well as to stimulate insulin secretion (improvement of beta cell dysfunction). If the beta cells are so severely damaged that they can no longer produce enough insulin, insulin must be injected from the outside, just like in type 1 diabetes.

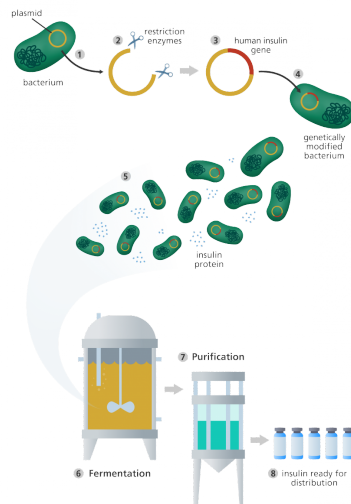
(<https://www.beobachter.ch/gesundheit/krankheit/diabetes-mellitus-zuckerkrankheit>)

There are many different types of treatments for people with diabetes, lack of insulin and recently Roche announced a new treatment, the "Patch Pumps". Those are stick-on insulin pumps that provide people with diabetes with insulin on a continuous basis. On July 23, 2018, Roche Diabetes Care announced that it has received the CE mark for the Accu-Chek Solo micropump. Accu-Chek Solo is a small, tubeless insulin pump system that allows people with diabetes to retrieve an insulin bolus directly at the pump or via the handheld. The system consists of two parts: a small, lightweight and partially reusable insulin micropump and a full-fledged remote control with integrated blood glucose monitoring and bolus suggestion calculator. It allows delivery of an insulin bolus both through the handheld and directly to the pump. In addition, the pump can be removed and reapplied without wasting insulin, according to the manufacturer.

(<https://www.roche.com/de/media/releases/med-cor-2018-07-23.htm>)

But that's just one way of treating diabetes, there are many other treatments.

## Technique



### The genetic engineering process

This treatment is relatively new. Until the 1980s animal insulin was the only available treatment for diabetes.

At first a DNA ring called a plasmid is extracted from the yeast cell or bacteria. Mostly *E. coli* is used. Then a small section is cut out of the plasmid by restriction enzymes, 'molecular scissors'. The gene for human insulin is inserted into the gap in the plasmid. The DNA ligase enzyme works as a glue that connects the plasmid with the gene, that codes for insulin. This plasmid is now genetically modified and gets introduced into a new bacteria or yeast cell, where it starts dividing rapidly and starts producing insulin. To create large amounts of the cells, the genetically

modified bacteria or yeast are grown in large fermentation vessels that contain all the needed nutrients. The more the cells divide, the more insulin is produced. When fermentation is complete, the mixture is filtered to release the insulin. The insulin is then purified and packaged into bottles and insulin pens for distribution to patients with diabetes.

<https://www.onlinebiologynotes.com/human-insulin-production-by-genetic-engineering/>

A different approach that needs to be mentioned is the approach, where the two amino acid chains, which are in the gene for insulin and connected through disulfide bonds, get synthesised individually and later on assembled.

[http://www.vivo.colostate.edu/hbooks/pathophys/endocrine/pancreas/insulin\\_struct.htm](http://www.vivo.colostate.edu/hbooks/pathophys/endocrine/pancreas/insulin_struct.htm)

<https://www.diabetes.co.uk/insulin/animal-insulin.htm>

<https://www.yourgenome.org/facts/what-is-genetic-engineering> bild

Thus now there are different types of insulin:

**Short acting insulin:** Their effect starts quickly and lasts only for a few hours.

**Long acting insulin:** These are mixed with a delay substance to prolong the duration of action of the insulin through a gradual absorption into the bloodstream.

## Interview

For the interview we met Jonas Rutishauser, a doctor in Basel who is specialised in endocrinology, which is about hormones and he also knows a lot about diabetology. In his profession among other things he also prescribes insulin, where it's necessary. We didn't take any pictures because anyone can imagine what a doctor's office looks like.

1. What aspects have to be kept in mind while choosing an appropriate insulin treatment?

The first step that has to be made is the differentiation between diabetes type 1 and 2. A patient with type 1 really needs the insulin to survive whilst someone with a type 2 diabetic won't get an insulin treatment right away. When it's the case, that diabetic with type 2 should receive insulin, the decision needs to be made whether the type 2 diabetic only needs as much insulin to cover the basal demand so a long acting insulin or even short acting insulin to have an insulin supply after meals.

2. When do you start prescribing insulin to a patient with diabetes type 2?

There are new medications which make it possible to postpone an insulin treatment. That's important because insulin also is a growth hormone, which transports amino acids and fatty acids into the cells, where they get stored. Through that phenomenon the fat loss is inhibited, although fat loss should be the goal of a type 2 diabetic. There is a conflict of interest, when giving insulin too early to a diabetic with type 2, because the fat gain supports insulin resistance thus resulting in a never ending vicious cycle. The more insulin is given, the higher is the fat gain. Nowadays there are some drugs that break that vicious cycle and lower the cardiovascular risk with diabetics. So lastly lifestyle interventions are the first step, which often show tremendous results, then drugs like metformin are used and only when that didn't work insulin gets prescribed.

3. What happens if diabetes is not treated? In type 1 and type 2?

With type 1 it can get dramatic within hours. The pH value decreases and there is much dehydration because of the loss of glucose. This leads to a ketoacidosis, which can cause death. On the other hand with diabetes 2 weight loss is the first thing that can be observed with no treatment, due to the insulin resistance. This can mistakenly be looked at as a good thing, but it only means the patient gets catabolic. After years with this condition, when the beta cells stop working, the same symptoms as in type 1 can occur.

4. What are the risks of overtreatment?

When diabetic type 2 receive large amounts of insulin to deal with the high glucose values and the bad eating habits, that most type 2 patients have, they gain a lot of weight. Like I said before this starts the vicious cycle. Another problem that both

types can have, is hypoglycemia, where the blood has not enough glucose due to overtreatment. In the past that was often the case because it was thought that normal values are healthier for those people. Ironically that is not the case. It actually slightly increases the mortality risk.

5. What factors rely on the patient only and not the doctor nor the insulin in regard of adherence?

Often diabetics with type 2 don't exercise enough and don't follow a healthy diet. Quite often older people can't execute the right treatment. For example taking the right pills at the right time or measuring the amount of glucose. There is also an increasing number of technical tasks, which come with increasing amounts of gadgets.

6. Are there still people who receive insulin from animals?

No. Nowadays only those drugs get prescribed, that were synthesised from yeast or bacteria from the humane sequence.

## Discussion

### PUMP THERAPY

A special form of insulin therapy is pump therapy. Short-acting insulin is delivered to the subcutaneous fat tissue via a catheter on a body-worn pump. A certain amount is automatically given regularly to cover the basal demand, in addition to the meals the bolus can be retrieved at the push of a button. Due to the more favorable effect profile, the analog insulins are becoming more and more prevalent in pump therapy. By programming, it is possible to customize the insulin supply. Nocturnal hypoglycemia and high blood sugar levels in the morning are easier to avoid. And at the same time, it is possible to respond well to irregular meals and to different movements through additional insulin doses - which makes the therapy much more stable in children.

#### Advantage:

1. Better blood sugars. First and foremost. Pump users tend to have lower A1C scores and less glucose variability (fewer "high to low" and "low to high" swings) than those on injections.
2. Fewer lows. By using only rapid-acting insulin, there is no long-acting insulin peaking or working too hard at inappropriate times. This makes pump therapy a good choice for those who have frequent lows, a history of severe lows, or a hard time detecting low blood sugars.
3. The pump therapy enables a more flexible lifestyle. The pump lets you choose your own schedule in regard of dieting, exercising and lifestyle.
4. Precise dosing. Pumps deliver insulin to the nearest .1, .05 or .025 units; ideal for those who are sensitive to very small doses, such as children and lean/active adults.

5. Convenience. There is no need to draw up syringes every time you need insulin; just reach to your pump and press a few buttons.

#### Disadvantages

1. Costs. Although most insurance plans cover insulin pumps and supplies, there are often co-pays and deductibles that must be met.
2. A learning curve. There, probably, won't be a good control right away. It usually takes a few months to get the basal and bolus doses regulated and to adjust to using the pump correctly.
3. Inconvenience. Wearing the pump around the clock, even during sleep, can become disturbing every once in a while.
4. Technical Difficulties. As mechanical devices, pumps are prone to occasional infusion set clogs, electronic failures, computer glitches and damage due to typical wear and tear.
5. Skin Problems. Skin can become irritated from infusion set adhesive, and infections can occur if infusion sets are worn too long or inserted improperly. Insulin absorption can be hindered if infusion sets are not changed regularly and sites are not rotated properly. (<https://www.medtronic-diabetes.co.il/en/what-insulin-pump-therapy>) (<https://www.diabetes.co.uk/insulin-pumps/pros-cons-of-insulin-pumps.html>)

### MULTIPLE DOSE INJECTIONS

Multiple dose injection (MDI) therapy, also known as multiple daily injections, is an alternative term for the basal/bolus regime of injecting insulin. The therapy involves injecting a long acting insulin once or twice daily as a background (basal) dose and having further injections of rapid acting insulin at each meal time. Multiple daily injection therapy will usually involve at least four injections a day.

#### Advantages

1. On multiple daily injections, there is more freedom as you don't need to plan so far in advance or be so restricted by injections delivered a number of hours ago.
2. Because MDI involves rapid acting insulin, it has allowed people to wait less time before eating after injecting.
3. Depending on the overall GI content of a meal, some people may be able to inject during or after a meal, without their blood sugar 'spiking' too much.
4. Generally speaking, rapid acting insulin helps to reduce the effect of high blood sugar levels 1-2 hours after eating.
5. Furthermore a multiple dose regime allows more flexibility as to when meals can be taken.
6. Injections tend to be cheaper.

#### Disadvantages

1. Multiple daily injections should be accompanied by a strong understanding of how the regime works particularly as rapid acting insulin can lead to faster onset of hypos if dosing errors are made.
2. A potential disadvantage of the extra freedom allowed by multiple daily injections can lead to more chances being taken, such as eating types or quantities of foods that one wouldn't eat on a twice daily regime.

3. Frequent needle sticks can cause injection areas to become resistant due to frequent injections.

<https://www.diabetes.co.uk/insulin/multiple-dose-insulin-injection-therapy.html>

A big change that was made in the field of treating diabetes is synthesising insulin instead of taking insulin from animal origin. Through that switch there are no more allergic reactions to the insulin. Strictly vegan diabetics can receive an insulin treatment with synthesised insulin in place of animal insulin. The last point that supports giving human insulin over animal one is that human insulin is actually the type of insulin, that humans should receive. Insulin from other species isn't made for human usage, because there are slight differences.

The interview with Mr. Rutishauser showed us how careful doctors have to be when choosing the right treatment and that they try not to prescribe insulin to a diabetic type 2 in an early stage. Instead, they try to counteract the metabolic syndrome by changing the habits of life. If that didn't work medication gets prescribed and only then the patient receives insulin.

An insulin therapy only works good, when the patient actually tries to do well and executes the treatment in a good manner. Pharmaceutical manufacturers can increase the overall adherence through creating a product, that's easy to use.

One thing we didn't expect was, that the problems with overtreatment would go up to this extent. Also the importance of treating diabetes came across. Overall we can say that it's highly difficult to reach that optimum of insulin, where it does its purpose without being harmful but the effect also isn't too low.

## Summary

The concentration of glucose in the blood is regulated by a control loop consisting of two hormones which are released depending on the blood sugar concentration. Insulin is the only hormone that can lower blood sugar levels. The other one is glycogen. If the body is not able to produce insulin or the cells build up a resistance, then the body suffers from a metabolic disease called diabetes. Through adding synthesised insulin to the patient's body, the blood sugar concentration can be lowered again.

Through various ways we found out how hard but also important it is to choose the right treatment for the patient.