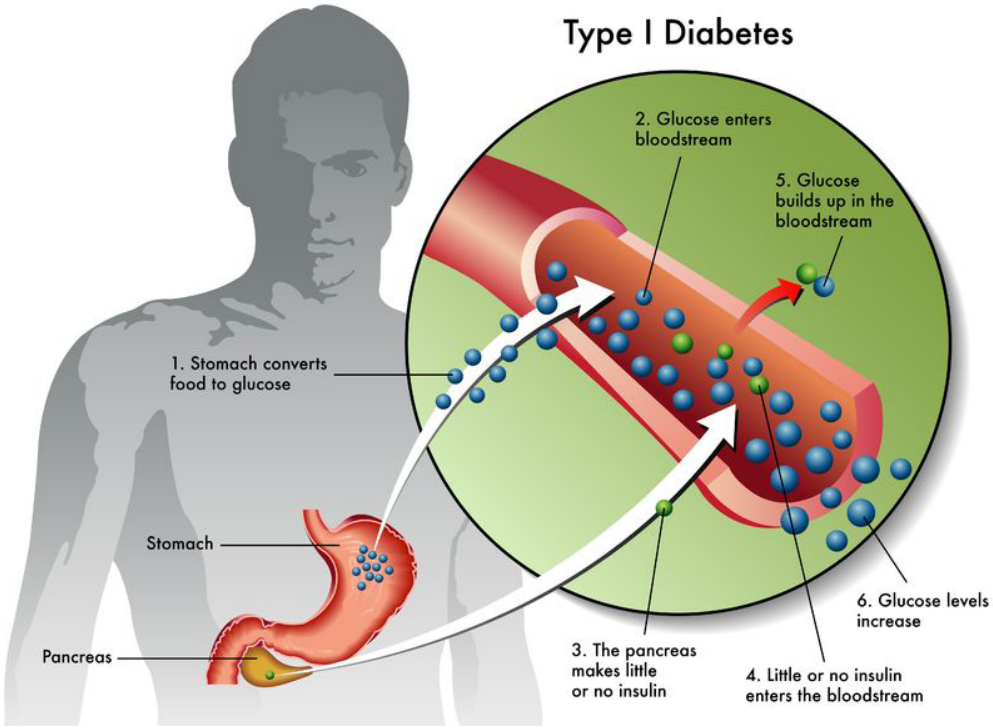
What is diabetes?

Diabetes mellitus, often shortened to “diabetes”, is a chronic condition that affects the body's ability to control blood sugar level and use energy from food. In a healthy body, carbohydrates from nutrition are broken down to glucose, which in turn provides energy for the cells. This process is controlled by a hormone called insulin. Diabetes is due to the inability of the body to produce enough insulin (Type 1 diabetes) or to use it properly (Type 2 diabetes). Consequently, glucose builds up in the blood stream. If left untreated, diabetes leads to serious health complications, including heart disease, kidney failure, nerve damage or blindness. The incidence of diabetes is increasing very rapidly. Worldwide, there are currently about 415 million people with diabetes, expected to grow to about 642 million diabetics by 2040 (*International Diabetes Federation, Diabetes Atlas, 2015*).

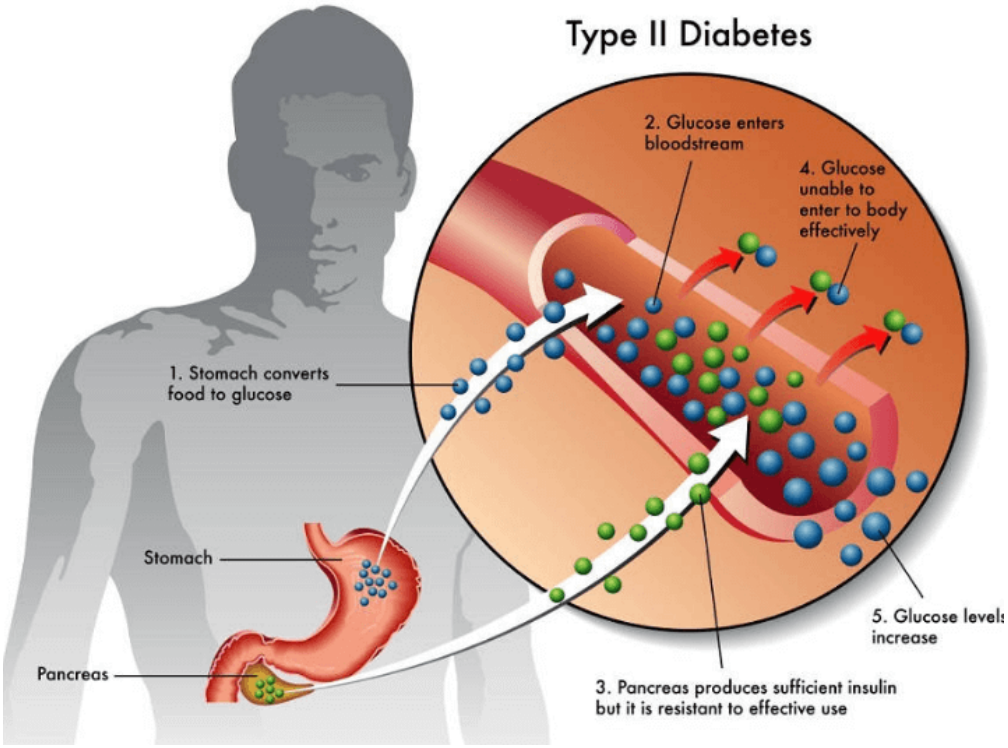
Type 1 diabetes

Type 1 diabetes, also known as insulin-dependent diabetes, usually develops in childhood or during adolescence and is due to faulty beta cells in the pancreas that normally produce insulin. There is often a genetic predisposition for Type 1 diabetes, and the disease accounts for about 10% of all diabetes cases. Treatment for Type 1 diabetes involves taking insulin, which is typically injected through the skin, often prior to or with meals. Once injected, insulin gets absorbed into the blood stream and reduces blood glucose to prevent its level to rise dangerously high (so called hyperglycaemia). It is critical that the amount of insulin injected is proportional to the amount of food eaten, and injecting too much insulin can lead to a blood glucose level that is dangerously low (so called hypoglycaemia). The appropriate management of Type 1 diabetes is thus a very fine balancing act between food intake and delivery of the right amount of insulin.



Type 2 diabetes

Type 2 diabetes, also known as non-insulin dependent diabetes, accounts for about 90% of all diabetes cases. It often develops in adulthood and is related to obesity, insufficient physical activity and unhealthy diet. With Type 2 diabetes, the pancreas typically produces some insulin, but either the amount produced is not sufficient or the body's cells, particularly liver and muscles cells, develop resistance to it. If diagnosed early the Type 2 diabetes can be managed through weight control, exercise and improved diet, and the condition can be in some cases reversed. Weight control in Type 2 diabetes is often managed using certain types of medication, such as GLP-1 receptor agonists. However, as the condition progresses diabetes medication, including insulin in a similar way to Type 1 diabetes, is typically required.



Insulin

The goal of diabetes treatment is to keep blood glucose levels in a healthy range so as to reduce the risk of organ damage and other complications that result from chronic hyperglycaemia. As mentioned above, insulin is a critical part of the diabetes treatment, particularly Type 1 diabetes. There are currently about 25 million insulin users today, this number expected to grow to 39 million by 2040 (*International Diabetes Federation, Diabetes Atlas, 2015*). Insulin is typically administered by subcutaneous injection in the abdomen. To ensure more effective treatment variety of insulins have been developed, including insulins that act very slowly and provide a steady basal level during the day (for example, insulin glargine) and insulins that act very rapidly to ensure an effective reduction of blood glucose after meals (for example, insulin aspart, insulin lispro or Fiasp which is the fastest acting insulin currently on the market). However, there is still a strong need for insulin products that act even more rapidly than the products currently on the market. Different delivery methods for insulin have also been developed over time to ensure convenience for the patients and the

best possible therapeutic outcomes. Traditional syringes are still used in some cases, but they have been gradually replaced by more convenient insulin pens that use pre-filled cartridges and a fine needle. In addition, insulin pumps that dispense insulin through flexible tubing to a catheter under the skin of the abdomen, are becoming increasingly popular and are believed to become the delivery method of choice in not too distant future. New generation pumps are currently being developed to ensure greater convenience by more discrete size and design as well as their useful connectivity to external devices such as smart phones. The key parameter that prevents development of truly miniaturised pumps is the size of the insulin cartridge. Therefore, there is a strong unmet critical need for concentrated insulin that would enable keeping a given amount of insulin in as small a volume as possible.

Glucagon

Glucagon is released by the pancreas in healthy individuals, and it has the opposite effect to that of insulin. It is released in response to low blood glucose and in situations where extra glucose is needed by the body, for example during vigorous exercise. If blood sugar levels fall dangerously low, for example due to an excessive insulin dose, a severe hypoglycaemic episode may occur. This is a potentially life threatening situation requiring emergency treatment with glucagon. Administration of therapeutic glucagon as a rescue treatment for severe hypoglycaemia is safe and effective, however, its use is challenging due to its low solubility and very poor stability in liquid solution. Thus, currently available glucagon rescue kits are only available in the form of a lyophilized powder, which requires the caregiver to perform a complex multi-step reconstitution procedure prior to administration in this highly stressful emergency situation. The reconstitution procedure can and does lead to handling errors and delayed administration of glucagon, resulting in sub-optimal treatment. This is a significant barrier to the use of the rescue kits with recent usability studies demonstrating that more than 80% of people failed to reconstitute properly and inject the recommended dose of glucagon. As a result, only 10-20% of high-risk patients own a glucagon emergency kit. A stable aqueous glucagon would considerably improve the convenience of the rescue kit use in emergency situations. In addition, a stable aqueous form of glucagon is critical requirement for the development of bi-hormonal pump systems that enable efficient control of blood glucose by continuous delivery of insulin and glucagon at precisely controlled rates.

Financial burden

The diabetes problem has become a global epidemic, placing a large financial burden on healthcare systems and society as a whole through the increased use of health services, loss of productivity and the long term support needed to overcome diabetes related complications, such as kidney failure, blindness or cardiac problems. The majority of countries spend between 5% and 20% of their total health expenditure on diabetes (*International Diabetes Federation, Diabetes Atlas, 2015*). In the UK, the costs of healthcare for diabetes and its complications are approximately £14 billion per year, which is about ten per cent of the NHS budget, this figure not including lost working days, early retirement and the wider societal impact. Therefore, innovative products that improve convenience of using diabetes medication and consequent compliance with the treatment regime have a great potential not

only to transform the quality of life of people with diabetes, but also bring about significant savings by reducing diabetic complications.

The future

Better treatments, that more closely mimic the insulin profile in healthy individuals, are needed both to improve the quality of life of those living with diabetes and also the wider costs to health services and society as a whole. A big step forward will be the introduction of a sophisticated type of hormone pump called the *artificial pancreas*. This device will monitor blood glucose and adjust insulin and glucagon levels just as the pancreas does in people without diabetes in order to maintain the normal blood glucose level. The artificial pancreas will remove the need for the constant checking of blood glucose levels that diabetics endure on a daily basis and it goes without saying that such a device should be as small and discrete as possible. It is also expected that the pump design will be continuously improved so that these devices become more discrete and easy to use than many of the pumps used today. The progress in the areas mentioned here would be considerably accelerated if certain types of products, such as ultra-rapid acting insulin, ultra-concentrated insulin or liquid glucagon became available. Many of these critical needs are addressed by Arecor's technology and Arecor's internal product pipeline.