



From Curiosity to Discovery

International Research & Development Press Conference

TYPE 2 DIABETES

Overview

Type 2 diabetes is the most common type of diabetes, accounting for 90 percent of the more than 180 million cases worldwide.¹ Diabetes is a serious global problem which kills more than 3.8 million people annually.² The situation is set to worsen with the total number of diabetes-related deaths estimated to increase by more than 50 percent over the next decade.¹

There have been a number of advancements for type 2 diabetes with new treatment modalities developed over recent years. Despite this, type 2 diabetes rates continue to increase and patients continue to be burdened by serious diabetes-related complications.^{2,3} Traditional therapies are failing to meet the demands of today's type 2 diabetes landscape and new effective and tolerable treatments are required.

To address this unmet need, Boehringer Ingelheim is committed to researching and developing new compounds. Two mechanisms that have shown particular promise are DPP-4 and SGLT-2 inhibitors.

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1. What is Type 2 Diabetes?

Type 2 diabetes is a chronic disease that occurs when body cells don't respond to insulin properly (insulin most often starts with a resistance) and the pancreas produces inadequate insulin for the body's increased needs (type 2 diabetes).⁴

Insulin opens the cells' glucose channels that let glucose move from the blood into the body's own insulin. This means that continuously higher insulin concentrations are needed to stimulate the uptake of glucose from the blood into peripheral cells, e.g. muscle cells to be used as an energy source.⁴

If the insulin does not have an effect any more, the glucose channels cannot open properly. At the beginning, the insulin producing cells in the pancreas (β -cells) cope with the increased demand simply by raising insulin production and secretion. Increasing insulin secretion, however, is not an infinite process. Later, when β -cells reach their limits and can no longer meet to the demand from the periphery, excess glucose builds up and remains in the blood. High blood glucose levels cause the health problems linked to diabetes, often referred to as diabetic increase, and the full picture of type 2 diabetes complications start to unfold.⁴

Unlike type 1 diabetes, which is an autoimmune disease that leads to the early destruction of the β -cells, type 2 diabetes develops on the background of an insulin resistance. Obesity is a major cause of type 2 diabetes as it can cause increased insulin resistance that again may develop into diabetes and accounts for approximately 90 percent of all type 2 diabetes cases.^{1,4,5} Until recently, type 2 diabetes only occurred in adults; however, it is now also occurring in obese children.²

The incidence of diabetes is increasing at an alarming rate. In addition to obesity, the risk factors that contribute to this include:^{2,3}

- Ageing population
- Ethnicity
- Unhealthy diet
- Lack of physical activity
- Family history (inheritable genetic condition)

A contributing factor to the increase of type 2 diabetes is a global change in traditional lifestyles and dietary patterns. Diabetes rates are high in urban areas and are set to increase due to rapid industrialisation in many developing and developed countries.²

2. Complications of Type 2 Diabetes

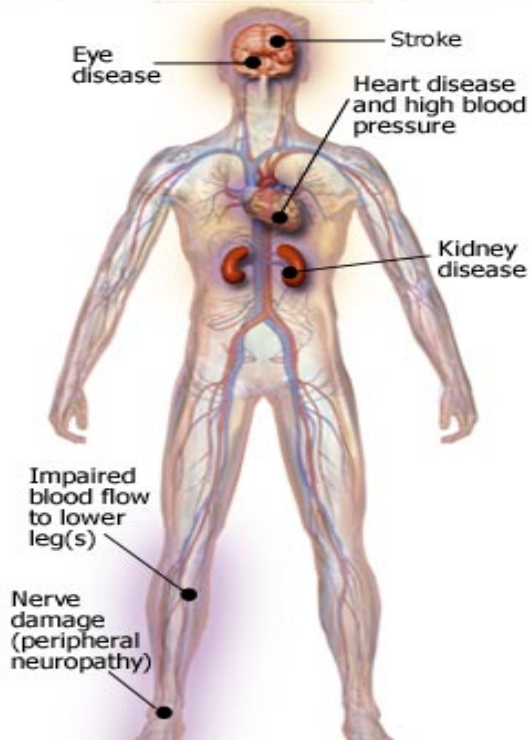
If high blood sugar (hyperglycaemia) is left uncontrolled, it can lead to serious medical complications to all parts of the body, especially where nerves and blood vessels play a vital role.² Because of its associated complications, diabetes is currently the most frequent cause of loss of vision, renal failure and amputation in the industrialised world.⁶ Diabetes is also associated with a two to five fold increase in the risk of heart attacks.⁶

Serious complications associated with uncontrolled type 2 diabetes include:⁷

- **Heart Disease and Stroke:** Diabetes causes an increased risk for heart attacks and stroke.
- **Kidney Disease:** Diabetes can damage the kidneys. Twenty to forty percent of diabetic patients have diabetic nephropathy and diabetes is the most frequent cause of end stage renal disease and dialysis in the Western World.⁴
- **Eye Complications:** People with diabetes often develop diabetic retinopathy (changes in the retina of the eye) and have a higher risk of blindness.
- **Diabetic Neuropathy and Nerve Damage:** One of the most common complications of diabetes is diabetic neuropathy damage to the nerves that run throughout the body, connecting the spinal cord to muscles, skin, blood vessels, and other organs.
- **Foot Complications:** Diabetes patients can develop different forms of foot problems. Foot problems most often happen when there is nerve damage in the feet or due to poor circulation. These problems are especially severe when nerve damage and poor circulation coincide.
- **Skin Complications:** Up to 30 percent of diabetes patients will have a skin disorder caused or affected by diabetes at some time. Skin complications can be the first sign that someone has diabetes.

Diabetes-related Complications

Over time, high levels of blood sugar can lead to the following:



Above: Diabetic foot ulcers

Below: Diabetic dermopathy



3. Treatment Options

The need for better therapeutic options for type 2 diabetes treatment is evident in view of the rapidly growing number of people affected. Novel type 2 diabetes treatments need to be safer, more tolerable, more efficacious and need to reduce the progression to disease.

Effective and balanced treatment is essential for the long-term health of those living with type 2 diabetes. Finding a successful treatment regime can be challenging and usually involves a process of trial and improvement. That said, treatment responses vary depending on the individual and the availability of more treatment options may result in a more tailored treatment in the future (depending on appropriateness of mode of action and potential limitations through side effects).

A significant proportion of type 2 diabetic patients treatments are not successful in helping them reach their targets and glycaemic control often deteriorates over time resulting in the necessity to start insulin therapy. Good diabetes control means keeping blood sugar levels as close to normal as possible. This can be achieved by a combination of diet control, exercise, home blood glucose testing and antidiabetic medication.

ESTABLISHED ANTIDIABETIC DRUGS

There are several treatments available for type 2 diabetics:

- **Metformin**⁸
One of the most widely-used drugs for type 2 diabetes – it works by reducing liver release of blood glucose from glycogen stores and by increasing cellular uptake of glucose in body tissues. Use of metformin is often limited due to gastrointestinal side effects such as bloating or diarrhoea. In addition, metformin is contraindicated in patients with impaired renal function.
- **Sulfonylurea**⁴
The most commonly used group of drugs. They increase glucose stimulated insulin secretion by the pancreas and lower blood glucose, even when insulin resistance is present. However, sulfonylurea drugs often lead to weight gain and are associated with a significant increase in the risk of hypoglycaemia (too low blood sugar levels).

Over recent years, a number of newer drugs have come to market. These include:

- **Thiazolidinediones (TZDs)**⁴
TZDs increase tissue insulin sensitivity by affecting gene expression. TZDs often lead to weight gain and have been shown to increase the risk of distal limb fractures in women. TZDs are contraindicated in patients with heart failure.
- **α -glucosidase inhibitors**⁴
These interfere with absorption of some glucose containing nutrients, reducing (or at least slowing) the amount of glucose absorbed. These drugs are often associated with gastrointestinal side effects and may be limited in the degree of blood glucose lowering compared to other anti-diabetic treatments.
- **Meglitinides**⁴
Stimulate insulin release quickly; they can be taken with food, unlike the sulfonylureas which must be taken prior to food. Meglitinides can result in weight gain and an increased risk of low blood sugar.
- **GLP-1 Analogues**⁴
Injectable medication, stimulates insulin release and furthermore reduces food consumption through

If antidiabetic drugs begin to fail, patients may require **insulin therapy**. Insulin can be used in combination with oral medication therapy to help keep glucose levels as low as possible.^{4,9} Approximately 40 percent of people with type 2 diabetes require insulin injections.

Finding and adhering to an effective treatment regimen is a life-long commitment for people with type 2 diabetes. Effectively controlling their diabetes helps to prevent and delay the progression of the serious complications associated with diabetes. In fact, a major study showed a 33 percent reduction in death from long-term complications when blood glucose was kept at a 'normal' level.

Despite innovation in diabetes treatments over recent years, incidence continues to rise rapidly, indicating that new therapeutic options are still needed. More than ever, patients require effective and tolerable treatment options. (For more information on developments of promising compounds for the treatment of type 2 diabetes, please see the "In the Pipeline: Future Treatments" background.)

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