

## **Type 2 Diabetes (T2D) Risk Factors**

T2D is the most common type of diabetes representing approximately 90% of all cases and most of these are adults. However, there is an increased incidence of type 2 diabetes in youth mainly due to sedentary lifestyle, less healthy food, and obesity which is the major reason behind insulin resistance responsible for type 2 diabetes. The American Diabetes Association recommends screening for type 2 diabetes in overweight children and adolescents.

T2D is characterised by insulin resistance, this occurs when the body produces insufficient insulin and/or does not use it properly.

Insulin resistance is when cells in your muscles, fat, and liver don't respond well to insulin and can't easily take up glucose from your blood. As a result, your pancreas makes more insulin to help glucose enter your cells. As long as your pancreas can make enough insulin to overcome your cells' weak response to insulin, your blood glucose levels will stay in the healthy range.

Prediabetes occurs when your blood glucose levels are higher than normal but not high enough to be diagnosed as diabetes. Prediabetes usually occurs in people who already have some insulin resistance or whose  $\beta$ -cells in the pancreas aren't making enough insulin to keep blood glucose in the normal range. Without enough insulin, extra glucose stays in your bloodstream rather than entering your cells. Over time, this can develop into T2D.

T2D is associated with obesity, a lack of physical activity and smoking. If left untreated over time the extra demands on the pancreas to produce insulin can lead to a loss of insulin producing cells ( $\beta$ -cells). When this occurs people with type 2 diabetes will then need to take insulin injections to manage their blood sugar levels, thus developing Insulin Dependent Diabetes.

## **T2D Symptoms**

The onset of T2D is usually slow with many symptoms identical to Type 1DM, and can produce symptoms such as polydipsia (excessive thirst), polyuria (excessive passing of urine), enuresis (involuntary urination), lack of energy, extreme tiredness, polyphagia (excessive eating or appetite), slow-healing wounds; and also include recurrent fungal infections in the skin, tingling or numbness in the hands and feet.

## **T2D Therapy and Management**

Intensive lifestyle modification, pharmacology (drug treatment) or both can reverse, delay or prevent type 2 diabetes. The main treatment for T2DM is healthy lifestyle adopting a healthy diet, increased physical activity, smoking cessation and maintenance of health body weight.

Management of obesity: 60% of patients with type 2 diabetes are obese (body-mass index [BMI]  $\geq 30$ ) and show insulin resistance. Obesity is addressed by lifestyle modification, although drug therapy, very low-calorie diets, and bariatric surgery might also be considered.

If attempts to change lifestyle are inadequate to manage blood glucose levels oral medication is initiated with metformin the most common except for contraindications such as renal impairments. Multiple drug combinations may be used for the management of the blood glucose levels of patients with Type 2 Diabetes inclusive of GLP-1 agonists, SGLT2 inhibitors, DPP4 inhibitors, sulphonyl ureas, thiazolidinediones and alpha-glucosidase inhibitors.

Metformin: Metformin reduces hepatic glucose output, enhances peripheral tissue sensitivity, and stimulates GLP-1 secretion. Furthermore, metformin effectively lowers HbA1c concentration by about 1–2%, is weight neutral, does not cause hypoglycaemia, and can have modest beneficial effects on blood pressure and lipid profile.

GLP-1 agonists: GLP-1 agonists trigger GLP-1-like effects, which include increased insulin secretion, reduced glucagon secretion, reduced hepatic glucose output, delayed gastric emptying, and increased satiety (feeling of fullness). GLP-1 receptor agonists are either long-acting

(dulaglutide, albiglutide, liraglutide) or short-acting (exenatide, lixisenatide) drugs that are given once weekly or once or twice daily. This class of drugs is effective, with reductions in HbA1c concentration of about 1% and weight loss of up to 4 kg. The risk of hypoglycaemia is low unless combined with sulfonylureas or insulin.

SGLT-2 inhibitors (dapagliflozin, canagliflozin, empagliflozin) are the latest glucose-lowering agents to become available. These drugs increase urinary glucose excretion by inhibiting SGLT-2 in the renal proximal tubule. These drugs do not cause hypoglycaemia (too low blood glucose) unless combined with sulfonylureas or insulin.

Dipeptidyl peptidase-4 inhibitors (gliptins): DPP-4 inhibitors are oral agents that inhibit activity of the enzyme DPP-4 and hence prolong the actions of endogenous GLP-1. Three DPP-4 inhibitors are currently available: sitagliptin, vildagliptin and saxagliptin. All have been shown to be effective at lowering HbA1c by nearly 0.7 to 1%.

Sulfonylureas, such as gliclazide and glimepiride, act on  $\beta$  cells to stimulate insulin secretion and, as a consequence of established efficacy and low cost, are often the first choice for dual therapy. However, these drugs are associated with hypoglycaemia (up to six times increased risk compared with metformin) and weight gain, and concerns remain with respect to an association with adverse cardiovascular disease outcomes.

Bariatric Surgery is emerging as a successful option for the treatment of obesity and type 2 diabetes. There is accumulating evidence that surgery with gastrointestinal manipulations may result in T2DM remission. Bariatric surgery has been shown to improve glucose homeostasis (stable steady level) by reducing insulin resistance and increasing insulin secretion.