Monogenic diabetes includes predominantly early-onset forms of diabetes that are caused by a single genetic change that affects pancreatic islet development or function, including neonatal diabetes, maturity-onset diabetes of the young (MODY) and various diabetes-associated syndromes.

**Epidemiology**

The true prevalence of monogenic diabetes is difficult to ascertain because of phenotypic overlap with other forms of diabetes, limited awareness of this condition among health-care providers and insufficient genetic testing (even in resource-rich settings), resulting in a majority of cases potentially going undiagnosed. Neonatal diabetes occurs in 1 in 90,000 live births, MODY could comprise 0.5–5% of non-autoimmune diabetes diagnoses and prevalence is estimated at 100 cases per million people. Genetic sequencing has revealed that some people with apparent type 2 diabetes mellitus (T2DM; with age of onset >40 years) actually have monogenic diabetes. In this population, mutated genes include those that could influence insulin secretion or function, including neonatal diabetes, maturity-onset diabetes, and insufficient genetic testing (even in non-European populations, such as in Asia and Africa). Management mostly relies on established treatments, so identifying these carriers is important.

- The reduced cost of next-generation sequencing could facilitate genetic screening for monogenic diabetes in patients with early-onset diabetes and their first-degree relatives.

**Diagnosis**

Monogenic diabetes typically occurs with early onset (<30 years of age), without obesity or overweight, with mild hyperglycaemia at disease onset, and a strong family history of diabetes. This pattern is distinct from that in type 1 diabetes mellitus (T1DM), which is associated with autoimmunity and insulin requirement at diagnosis, and T2DM, which is usually accompanied by obesity and insulin resistance and associated features. Diagnosis is confirmed using genetic sequencing, either of a panel of established monogenic diabetes genes or whole-exome sequencing, although these approaches lack sensitivity to detect copy-number variations or identify mitochondrial DNA mutations.

- Monogenic diabetes is caused by rare pathogenic mutations in various genes, with different patterns of inheritance. Mutations in some of these genes can also cause apparent T1DM or T2DM.

**Mechanisms**

Monogenic diabetes gene products function in multiple compartments of pancreatic β-cells, including the nucleus, cytoplasm, plasma membrane, mitochondria, endoplasmic reticulum and insulin granules.

Monogenic diabetes is associated with different patterns of inheritance. Diagnosis is confirmed using genetic sequencing or genetic change that affects pancreatic islet development or function, including neonatal diabetes, maturity-onset diabetes of the young (MODY) and various diabetes-associated syndromes.

**Management**

Treatment of monogenic diabetes must take into account the underlying pathogenic mutation. For example, insulin therapy is not appropriate in people with GCK mutations, as insulin production is unaffected. Indeed, fasting hyperglycaemia is mild and diabetes complications typically do not occur in these patients, so treatment is unnecessary except in pregnancy. Management can involve sulfonylureas, which stimulate insulin secretion by pancreatic β-cells, with the dose determined by the underlying pathogenic mutation (for example, low dose for diabetes caused by HNF1A or HNF4A mutations, and high dose for diabetes caused by KCNJ11 or ABCC8 mutations). Lifestyle and dietary recommendations for monogenic diabetes are similar to those for T1DM or T2DM, including moderate physical activity and a balanced diet. Some forms of monogenic diabetes require close monitoring for the development of serious pancreatic or extra-pancreatic manifestations, such as cardiac problems (GATA4 and GATA6 mutations) and neurodevelopmental issues (KCNJ11 or ABCC8 mutations).

**Outlook**

Research on monogenic diabetes has improved understanding of the pathogenesis of diabetes in general, although further progress is needed. Widespread, accurate, rapid and inexpensive genetic sequencing is needed to facilitate diagnosis worldwide, as well as to improve knowledge of monogenic diabetes pathogenesis in non-European populations, such as in Asia and Africa. Management mostly relies on established treatments, so research on pancreatic β-cell biology and defects in monogenic diabetes is needed to facilitate the development of new, pathogenesis-specific treatments.