TYPE 2 DIABETES

Post Graduate Excellence Program

Module 1

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Type 2 diabetes: A global health challenge

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INTRODUCTION

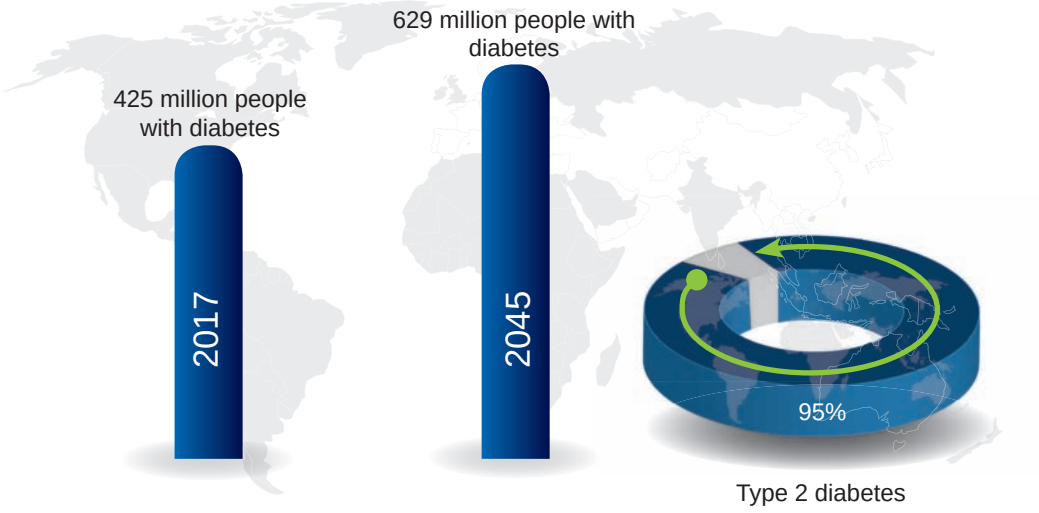
Type 2 diabetes mellitus is a metabolic disorder characterized by the presence of chronic hyperglycemia due to underlying insulin resistance coupled with defective insulin secretion. The disease often remains undetected for many years as large number of patients with diabetes remain asymptomatic until the late stage of the disease resulting in advanced complications and increased health care cost.[1]

The prevalence of diabetes is rapidly rising at an alarming rate and has reached epidemic levels globally. Given the modern lifestyle and rising prevalence of obesity, the past few decades have witnessed a tremendous escalation in the prevalence of diabetes mellitus, especially type 2 diabetes, making this a preeminent global heath challenge.[2,3] Latest data from the International Diabetes Federation (IDF) estimate that 425 million people worldwide are diabetic and the prevalence is likely to rise to 629 million by the year 2045.[4] Yet, almost 46% of all diabetes cases remain undiagnosed globally.[5] Type 2 diabetes accounts for nearly 95% of all cases of diabetes with burgeoning incidence reported in developing countries (figure 1).[1] Recent figures provide an estimate of the substantial public health threat posed by the escalating prevalence of diabetes and its major economic impact on the health care system. This reinforces the importance of employing effective disease management strategies.[6]

NATURAL HISTORY OF TYPE 2 DIABETES

Genetic susceptibility and other risk factors like obesity and physical inactivity contribute to decreased insulin sensitivity in individuals predisposed to develop diabetes. Pancreatic islet cells adapt to insulin resistance by increasing pancreatic beta-cell

Figure 1 **Estimated escalation in the global prevalence of diabetes mellitus**



Based on information from:

1. American Diabetes Association. Standards of Medical Care in Diabetes—2018. *Diabetes Care*. 2018;41(Supplement 1).
2. IDF Diabetes Atlas – 8th Edition. Available at: http://www.diabetesatlas.org/across-the-globe.html. Accessed Feb 20, 2018.

mass and enhancing function, thus causing compensatory hyperinsulinemia. Providing beta-cells release of insulin remains sufficient to offset insulin resistance, glucose homeostasis is maintained and glucose tolerance remains normal. When beta-cells fail to adequately compensate for insulin resistance, impaired glucose tolerance (IGT) develops. Sequential increase in plasma glucose, first postprandial and then fasting leads to overt diabetes. It is then recognized that beta-cell failure presents much earlier in the course of disease than previously thought, and is well advanced by the time diabetes is diagnosed clinically.[7,8] Studies suggest that at the diagnosis of diabetes almost 80% of beta-cell function is lost. Approximately half of patients with diabetes develop diabetes-related complications.[9-11]

Once hyperglycemia is apparent, beta-cell function further deteriorates with subsequent exacerbation of insulin resistance.[12,13] Progressive beta-cell failure contributes to worsening of glycemic control and development of diabetic complications. Results from the longitudinal United Kingdom Prospective Diabetes Study (UKPDS) showed that, irrespective of the therapeutic interventions, patients with type 2 diabetes exhibit progressive increase in glycemia concomitantly with the decline in beta-cell function.[14] This was further corroborated by recent findings from the Insulin Resistance Atherosclerosis Study which confirmed that continuous decline in beta-cell function measured by homeostasis model assessment was more pronounced than previously thought and is the key driver of disease progression.[15] Surpassing insulin resistance, impaired insulin secretion due to loss of beta-cell function is the underlying defect in the development of type 2 diabetes and determines the rate of disease progression.[7]

PATHOPHYSIOLOGICAL MECHANISMS IN DEVELOPMENT AND PROGRESSION OF TYPE 2 DIABETES

As discussed above, the two core pathogenic mechanisms implicated in the development of type 2 diabetes are insulin resistance with its diminished metabolic response and deficient compensatory beta-cell insulin secretion resulting in hyperglycemia.[16]

Several genetic and environmental factors like obesity and physical inactivity greatly contribute to the insulin resistant state.[16] Insulin resistance develops primarily in skeletal muscle, liver and adipose cells.[7,17] In the liver, despite the elevated fasting insulin level, resistance to the action of insulin results in impaired suppression of hepatic glucose production, which, with other metabolic factors