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*Clinical Insights from a Diabetes Progression Model*

Insulin is the chief hormone that regulates glucose homeostasis, preserving glucose for use by the brain in fasting conditions but sharing glucose with other tissues, such as muscle, after meals. This orderly cycle of fuel usage is disrupted in obesity, which renders tissues resistant to the effects of insulin and leads to chronic hyperglycemia, a condition known as type 2 diabetes. A salient characteristic of diabetes is its relentless progressive nature, which is almost impossible to reverse once the disease is established and difficult to reverse in the pre-diabetes stage when glucose is elevated but below the diagnostic threshold. A puzzling feature is that people with pre-diabetes or in the early stages of T2D have abnormally high plasma insulin concentrations, and insulin rises before glucose does. We show that these characteristics of diabetes are explained by a mathematical model in which the onset of T2D is represented by the crossing of a threshold. From a clinical point of view, the near irreversibility of diabetes once the threshold is crossed highlights the need for identifying people at risk early. We will present examples of how the model has provided insights for improving diabetes screening and treatment.