individual becomes more insulin resistant (by moving from point A to point B), insulin secretion increases. A failure to compensate by increasing the insulin secretion results initially in impaired glucose tolerance (IGT; point C) and ultimately in type 2 DM (point D). NGT, normal glucose tolerance. *(Data from SE Kahn: Clinical review 135: The importance of beta-cell failure in the development and progression of type 2 diabetes. J Clin Endocrinol Metab 86:4047, 2001 and RN Bergman, M Ader: Free fatty acids and pathogenesis of type 2 diabetes mellitus. Trends Endocrinol Metab 11:351, 2000.)*

Metabolic Abnormalities Insulin resistance, the decreased ability of insulin to act effectively on target tissues (especially muscle, liver, and fat), is a prominent feature of type 2 DM and results from a combination of genetic susceptibility, obesity, and metabolic inflammation. Insulin resistance is relative, however, because supranormal levels of circulating insulin will normalize the plasma glucose. In type 2 DM, both insulin potency and efficacy are reduced leading to an overall decrease in glucose utilization under many conditions (30–60% lower than in normal individuals). Insulin resistance impairs glucose utilization by insulin-sensitive tissues (skeletal muscle) and in liver, coupled with elevated glucagon, leads to increased hepatic glucose output. Increased hepatic glucose output predominantly accounts for increased FPG levels, whereas decreased peripheral glucose utilization results in postprandial hyperglycemia.

The precise molecular mechanism leading to insulin resistance in type 2 DM has not been elucidated. Insulin receptor levels and tyrosine kinase activity in skeletal muscle are reduced, but these alterations are most likely secondary to hyperinsulinemia and are not a primary defect. Therefore, “postreceptor” defects in insulin-regulated phosphorylation/dephosphorylation appear to play the predominant role in insulin resistance. Abnormalities include the accumulation of lipid intermediates within skeletal myocytes, which may impair mitochondrial oxidative phosphorylation and reduce insulin-stimulated mitochondrial ATP production. Impaired fatty acid oxidation and lipid accumulation within skeletal myocytes also may generate reactive oxygen species such as lipid peroxides. These and other mechanisms also generate low-grade metabolic inflammation that feeds back and directly worsens insulin resistance.