Non-invasive prediction of beta cell mass in type 2 diabetes: insights from a mathematical model.

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Abstract:

Diabetes results when beta cell mass (BCM) and insulin secretion are insufficient to control plasma glucose. Maintenance or growth of BCM is therefore an important therapeutic goal, but BCM is not directly measureable in humans. Various non-invasive predictors of BCM and pancreatic function have been proposed, including HOMA-beta, fasting glucose, 2-h glucose post OGTT, 15-min c-peptide/glucose post OGTT, plasma insulin, and fasting plasma proinsulin. We assessed how these predictors are quantitatively related to BCM and pancreatic function during the progression and treatment of diabetes. We expanded a previously validated mechanistic mathematical model of type 2 diabetes to include BCM dynamics (replication and apoptosis). The model includes insulin, glucagon, glucose, and incretin metabolism and the pharmacokinetic and pharmacodynamic properties of antidiabetic therapies (GLP-1 agonists, DPP-4 inhibitors). Virtual patients (VP, n=300) exhibit a wide range in fasting plasma glucose (85-262 mg/dL), insulin (17-448 pM), and C-peptide (154-1736 pM). BCM was assumed to regulate the maximum insulin synthesis rate, and the VP cohort had a range of maximum insulin synthesis rates of 15-150% of normal. A 14-d clinical trial with drug or placebo, followed by a meal test (MMTT) on day 14, was simulated. Results showed that fasting plasma glucose (r=-.52) and fasting plasma C-peptide (r=.39) or log C-peptide/glucose ratio (r=.56) correlated significantly with BCM or maximum insulin synthesis rate. Insulin measures did not correlate with BCM, consistent with Breuer, et al (2010). C-peptide (r=.72), glucose (r=-.40) AUC and change in glucose AUC (r=.70) correlated with BCM. Representation of BCM dynamics in a mathematical model of diabetes identified potential non-invasive predictors of BCM and the underlying mechanistic rationale for each predictor. These results suggest that modeling may provide an improved approach to develop and validate biomarkers of BCM.