A Mathematical Model of the Pathogenesis, Prevention, Reversal of Type 2 Diabetes, and Clinical Implications

Type 2 diabetes (T2D) is generally thought to result from the combination of 2 metabolic defects, insulin resistance, which increases the level of insulin required to maintain glucose within the normal range, and failure of insulin-secreting pancreatic β-cells to compensate for the increased demand. Blood glucose and insulin concentrations fluctuate at fast timescales (hour) in response to daily meals. Two aspects of β-cell function operate on intermediate time scales (month). The dynamics of β–cell mass responds on slow timescales (year-decade). Based on this physiological system with multiple timescales, we built a mathematical model to elucidate how compensation succeeds or fails. The model quantifies the relative contributions of insulin action and insulin secretion defects to T2D and explains why prevention is easier than cure (see Fig). The latter is a consequence of a threshold separating the normoglycemic and diabetic states (bistability), which also underlies the success of bariatric surgery and acute caloric restriction in rapidly reversing T2D (see Fig). Finally, the model has been used to explore pathways of T2D and understand clinical data from Seoul National University Hospital Bundang.

Fig. Summary of the model

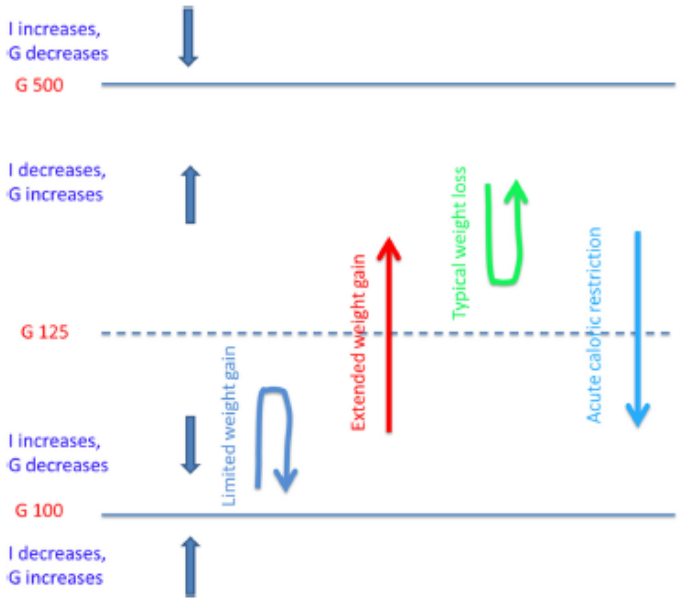

Fig: Schematic of model structure showing coexistence (bistability) of normoglycemic and diabetic states. Decreases in insulin sensitivity S_I tend to push glucose up, and increases in S_I tend to push glucose down. Below threshold (nominally 125 mg/dl glucose), the intrinsic dynamics increase I to counteract the effects of decreased S_I, whereas above threshold they reduce I and amplify the effects of decreased S_I.

References

1. A Mathematical Model of the Pathogenesis, Prevention and Reversal of Type 2 Diabetes, Endocrinology. 2016 Feb;157(2):624-35, **Endocrinology**
   Joon Ha, Leslie Satin, and Arthur Sherman.

2. Chronic glucose exposure systematically shifts the oscillatory threshold of mouse islets: Experimental evidence for an early intrinsic mechanism of compensation for hyperglycemia, 2016 Feb;157(2):611-23, **Endocrinoogy**
   Eric Glynn, Benjamin Thompson, Shusheng Lu, Suryakiran Vadrevu, Robert T.Kennedy, **Joon Ha**, Arthur Sherman and Leslie S. Satin

3. Pulsatile insulin secretion, impaired glucose tolerance and type 2 diabetes, **Molecular Aspects of Medicine**, 2015 Apr;42:61-77
   Leslie Satin, Peter Butler, **Joon Ha** and Arthur Sherman.

4. Hemoglobin Glycation Index is Independently Associated with Cardiovascular Diseases in People with Impaired Glucose Metabolism: Analysis of a Prospective Patient Registry, under review, **Annals of Internal Medicne**
   Chang Ho Ahn, See Hee Min, Dong-Wha Lee, Tae Jung Oh, Kyoung Min Kim, Jae Hoon Moon, **Joon Ha**, Arthur Sherman, Sung Hee Choi, Kyong Soo Park, Hak Chul Jang, and Soo Lim.

5. Prediabetes with high 30 minutes postprandial plasma glucose levels had β-cell dysfunction and insulin resistance similar to over type 2 diabetes and showed the rapid transition to future type diabetes, **In preparation**, to be submitted to **Diabetes**, Kyong Yeun Jung, Jie Eun Lee, Won sang Yoo, Eu Jeong Ku, Yun Ji Kim, Kyoung Min Kim, Jae Hoon Moon, Soo Lim, **Joon Ha**, Arthur Sherman, Hak Chul Jang, Sung Hee Choi

6. One-hour Postload Plasma Glucose Concentration in People with Normal Glucose Homeostasis Predicts Future Diabetes Mellitus: A 12-Year Community-based Cohort Study. **In Preparation**,
   Tae Jung Oh, Soo Lim, Kyoung Min Kim, Jae Hoon Moon, Sung Hee Choi, Young MinCho, **Joon Ha**, Arthur Sherman, Kyong Soo Park, Hak Chul Jang, Nam H. Cho