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A unified model of pathogenesis pathways of Type 2 diabetes

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Title: A unified model of pathogenesis pathways of Type 2 diabetes

We have developed a mathematical model for the mechanistic defects that underlie observed pathologies that lead to type 2 diabetes (T2D), such as impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). We have applied the model to study the natural history of progression to T2D as reported in the Baltimore Longitudinal Study of Aging (BLSA). It has been suggested that IGT is associated with peripheral insulin resistance and IFG with hepatic insulin resistance. We tested this by simulating subjects on a continuum from high peripheral resistance/low hepatic resistance to low peripheral resistance/high hepatic resistance. The model simulations confirm that association. The simulations show further that those who present first with IGT will progress to combined glucose impairment (CGI, i.e. IGT and IFG) and then to T2D, provided insulin secretion is sufficiently impaired.   Those presenting first with IFG similarly tend to exhibit CGI on the path to T2D. The BLSA study raised the question of whether CGI is an obligatory stage between IGT and T2D.   The model indicates that at the extreme of high peripheral resistance/low hepatic resistance, they may proceed directly from IGT to T2D without experiencing CGI. In other words, two-hour glucose may exceed the threshold for T2D while fasting glucose remains normal. This shows the importance of not basing T2D diagnosis solely on fasting glucose, but rather to also use oral glucose tolerance tests or possibly HbA1C. In summary, the model is able to recapitulate the diverse pathways to T2D that are seen clinically. Much of the natural variation can be captured simply by inversely varying peripheral and hepatic insulin resistance.   More detailed analysis that takes into account a second dimension of impairment in basal insulin secretion is needed to account for the diverse pathways seen in different ethnic populations.