COMMENT ON PICCININI AND BERGMAN

The Measurement of Insulin Clearance. Diabetes Care 2020;43:2296–2302

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We read with interest the review by Piccinini and Bergman (1) that *1*) argues for superiority of the Polidori-Bergman model or peripheral-portal infusion technique to estimate the metabolic clearance rate of insulin (MCR-I) over other methods, and *2*) hypothesizes that reduced MCR-I causes type 2 diabetes (T2D).

Obviously, the peripheral-portal infusion approach is not feasible in humans.

The Polidori-Bergman model allows one to estimate the MCR-I contribution of the liver and peripheral tissues. For reasons outlined below, we believe that some of the assumptions and constraints of this model adversely affect the accuracy of MCR-I estimation, especially during the fed state, such as an oral glucose tolerance test (OGTT).

The Polidori-Bergman model assumes that hepatic insulin extraction (HIE) is either constant or saturable, whereas extrahepatic insulin extraction is linear (assumed constant fractional insulin extraction). However, HIE does not reach saturability until the prehepatic insulin concentrations rise into the pharmacologic range, i.e., over 300–500 mU/L (2,3). Nonetheless, the authors retained this assumption since it provided the best data fit for their model, although not justified by experimental data (3)—an important limitation when estimating MCR-I.

Further, a variety of factors can affect HIE including the assumption that hepatic plasma flow is constant (e.g., 0.576 L/min/m^2), since during the OGTT hepatic blood flow changes markedly, despite a good fit of the data. Meal ingestion increases portal and reduces hepatic arterial plasma flow, which in turn increases systemic insulin levels by reducing hepatic insulin delivery during second pass. Thus, the sensitivity of MCR-I model estimates to changes in hepatic plasma flow during an OGTT needs to be tested.

Most importantly, while we agree with the authors that the MCR-I plays an important role in overall glucose homeostasis, we disagree that reduced MCR-I leads to T2D, a conclusion that is based upon measuring MCR-I under nonphysiologic conditions and with model assumptions that have yet to be validated, as discussed above. As discussed previously (3), when overt T2D is present, insulin resistance in muscle/liver/adipocytes, β-cell dysfunction, and reduced MCR-I are well established and it is impossible to discern which defect initiated the myriad of metabolic disturbances that characterize T2D.

We reported that MCR-I varies throughout the day (2), with a marked reduction from fasting to post–glucose ingestion. Obese subjects with and without T2D had lower oral glucose–induced suppression in MCR-I compared with lean individuals with normal glucose tolerance. Further, we reported that, despite a higher fasting MCR-I after bariatric surgery, compared with controls, these subjects had a much greater postprandial suppression in MCR-I (4). Among patients with bariatric surgery those with hypoglycemia after gastric bypass had the lowest prandial MCR-I (5). Collectively, these data indicate a significant variation in the physiologic signals that regulate hepatic/extrahepatic insulin extraction throughout the day; thus, a one-size-fits-all approach cannot address the contribution of changes in the MCR-I in health and disease. Moreover, it is impossible at the present state of knowledge to determine whether insulin resistance leads to a decrease in MCR-I or vice versa. Lastly, while reduced MCR-I and insulin resistance play an important role in the development of T2D, overt diabetes does not occur unless the β-cell failure ensues (6).

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