RESPONSE TO COMMENT ON PICCININI AND BERGMAN

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

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We thank Dr. Gastadelli and colleagues for their interest in our review article (1) and their comments (2) on the limitations of different approaches to assessing insulin clearance in humans and putative limitations of the hypothesis (3) that lower insulin clearance might cause type 2 diabetes (T2D). In fact, many of their comments relate to a series of articles from our group, and in addition to the article they refer to (1), several others (4–6) are also relevant to their comments.

Concerning the Polidori/Bergman model (4), they are correct that the approach used by Polidori et al. (4) assumes either linear or saturable hepatic insulin extraction and chooses the model that best fits the data. We believe these are reasonable assumptions and that there is little support for the claim by Gastadelli et al. (2) that a saturable model of hepatic insulin extraction is not justified based on experimental data. The articles they cite claiming that hepatic insulin extraction does not reach saturability until insulin concentrations are in the 300–500 mU/L range are based on comparisons between groups of two to three lean subjects, with high between-subject variability. Thus, no firm conclusions can be drawn from these limited data regarding when hepatic insulin clearance begins to saturate in lean subjects, much less in obese insulin-resistant subjects, who could have impairments in insulin receptor–mediated insulin uptake and degradation not present in lean subjects.

Further, their own study described in their letter shows that insulin clearance decreases in the postprandial state (when the rate of insulin delivery to the liver is high) compared with the fasting state. This finding could be due to hepatic insulin extraction being saturable (as assumed in the Polidori and Bergman model) and/or some other unknown physiologic regulation that acts to decrease insulin clearance in the postprandial setting in some individuals (as assumed by Gastadelli et al.). Either of these assumptions has the net effect of reducing insulin clearance during postprandial periods compared with fasting periods, and the Polidori and Bergman approach has the benefit of enabling the data to be well described using a limited number of parameters, whereas the Gastadelli approach essentially estimates clearance at each time point and provides no information on the contribution of hepatic versus extrahepatic clearance.

Their comments on changes in blood flow during postprandial periods are important, and the Polidori and Bergman modeling approach was originally developed using intravenous glucose tolerance tests (IVGTTs), where meal-induced changes in portal blood flow are not a concern. Changes in hepatic blood flow (if known) can be easily included in the modeling approach, and this issue was previously discussed in the Supplementary Material of reference 4, wherein we reported that most model parameters were very insensitive to variation in hepatic blood flow. In additional (unpublished) sensitivity analyses where we assumed postprandial increases in hepatic blood flow in the model during an oral glucose tolerance test, we observed virtually no change in the calculated total rates of hepatic and extrahepatic removal of insulin compared with when we assumed constant blood flow rates, whereas the calculated fractional extraction decreased when we assumed hepatic blood flow was increased.

Concerning the hypothesis regarding causation of diabetes by lower insulin clearance, Gastadelli et al. state that, "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." The hypothesis that reduced MCR-I might contribute to T2D pathogenesis was developed based on our research. In the IVGTT studies performed in African American adults by Gower and colleagues (5) and in children by Fernandez and colleagues (6), we concluded that hepatic (but not extrahepatic) insulin clearance is lower in African American adults and children than in European American adults and children. As African Americans are known to be at greater

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risk of developing T2D than European Americans and the reduced insulin clearance in African Americans is present even in normoglycemic adults and children, we hypothesized (3) that the reduced clearance could contribute to chronic hyperinsulinemia that could further lead to insulin resistance, additional compensatory insulin secretion, β-cell stress, and T2D. A recent study by Chang and colleagues provides direct support for the hypothesis that lower insulin clearance per se may be an important risk factor for developing T2D (7). In a longitudinal study of a population of 448 members of the Pima Nation of Arizona, followed up for almost 8 years, they found that lower insulin clearance (measured by euglycemic glucose clamps and not our modeling approach) was a risk factor for conversion to T2D, independent of insulin resistance or β-cell response. We believe that further studies are warranted to better understand and characterize the role of reduced insulin clearance in the pathogenesis and progression of T2D.

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