COMMENTS AND RESPONSES

Novel Noninvasive Breath Test Method for Screening Individuals at Risk for Diabetes

Response to Davidson

We thank Dr. Davidson (1) for his insightful alternative to the interpretation of our results (2). While the validity of the breath test method to distinguish between individuals with normal glucose tolerance (NGT) and pre-diabetes and early-stage diabetes (PDED) is not affected by this interpretation, he brings up a valid point that tracer dilution due to differences in fasting glucose may influence the appearance of $^{13}CO_2$ in breath. However, we argue that the shapes of the curves we obtained for NGT and PDED do not support this as the only explanation. We expect that a dilution effect by itself would have mainly affected the magnitude of the $^{13}CO_2$ peak—not the slope and time of peak $^{13}CO_2$ appearance. Furthermore, area under the curve data suggest that after 10 h there were no differences in appearance of glucose-derived CO_2, suggesting that the fate of glucose was not different between NGT and PDED.

We agree that the dysregulation of glucose clearance in PDED likely involved defects in both glycogen synthesis and glucose oxidation, which is supported by the vast literature on this topic (3–6). Though decreased uptake per se may have contributed to a shift in breath curves, we believe that decreased glycogen storage in PDED would have likely increased the availability of labeled glucose for oxidation, thereby compensated at least somewhat for the aforementioned dilution effect due to differences in blood enrichment.

Because we did not directly measure blood or glycogen enrichments, we agree that alternative explanations for the observed differences between glucose-derived $^{13}CO_2$ in NGT and PDED are possible. However, regardless of the ultimate fate of glucose in our subject groups, our method was able to make a clear distinction between NGT and PDED individuals, which was the primary objective of this project. We agree that many factors need to be considered to explain the observed differences in glucose-derived CO_2 kinetics (some mentioned in the article) and that there is a need for further research in this area.

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Acknowledgments— Please see ref. 2 for a list of the potential conflicts of interest relevant to this article.

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