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COMMENT ON FÆRCH ET AL.

GLP-1 Response to Oral Glucose Is Reduced in Prediabetes, Screen-Detected Type 2 Diabetes, and Obesity and Influenced by Sex: The ADDITION-PRO Study. Diabetes 2015;64:2513–2525

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On the basis of their Danish study population, Færch et al. (1) concluded that glucagon-like peptide 1 (GLP-1) response to oral glucose tolerance testing (OGTT) was up to 25% impaired in prediabetes and screen-detected diabetes compared with normal glucose tolerance (NGT) and more pronounced in women than men. This finding supports the concept introduced more than two decades ago that a diminishing incretin effect is associated with the development of type 2 diabetes (T2DM), with early impaired GLP-1 release occurring before rather than after diabetes becomes clinically manifest.

The authors cite the Baltimore Longitudinal Study of Aging (BLSA) (2), during which participants found to have developed T2DM (evidenced by both fasting and 2-h glucose levels) on an annual OGTT exhibited much higher intact and total GLP-1 plasma levels (after the first 20 min and up to the 80-min time point) and areas under the curve compared with those who continued to have NGT, concomitant with rising plasma insulin levels. This physiologically relevant insulinotropic effect of GLP-1 was associated with increased numbers of L phenotype duodenal endocrine cells in the newly diagnosed T2DM group, with no sex-specific difference.

The differences in GLP-1 excursions between BLSA and ADDITION-PRO participants are likely multifactorial but may be partially explained by the fact that ADDITION-PRO was not designed to capture newly diagnosed individuals with either prediabetes or T2DM. Thus, cross-sectional data derived from "screen-detected" T2DM could not be extrapolated further, as they might include individuals with long-standing diabetes, possibly on treatment. It has been established that long-standing T2DM is associated with reduced GLP-1 excursions, therefore inclusion of those individuals in the "screen-detected" group could significantly alter the results. Knowledge of characteristics regarding disease duration and prior therapy in individuals with T2DM, as well as post-OGTT concentrations of glucose-dependent insulinotropic polypeptide (GIP) across groups, could have been helpful.

In addition, the difference shown in GLP-1 concentrations and areas under the curve, which numerically only attain statistical significance when related to the 120-min time point post-OGTT, could argue against its direct involvement in modulating first-phase insulin secretion, underscored by similar insulin responses when GLP-1 secretion supposedly peaks at 30 min across groups.

Contrary to this study, further work on the annually monitored BLSA population has shown no difference in postglucose load intact or total GLP-1 excursions in individuals with newly diagnosed impaired glucose tolerance (3). In that group, much higher post-OGTT excursions of intact and total GIP were associated with hyperinsulinemia (4), suggesting a complex interplay between incretins—and possibly other factors—during progression toward T2DM.

Therefore, conclusions should be interpreted with caution, as possible dysregulation of incretin release or action in T2DM pathogenesis has not been firmly established. As growing interest has focused on the potential use of incretin-based therapies and other interventions in early stages of the disease, it is important that the pathophysiology

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of progressive glucose intolerance toward diabetes is fully elucidated.

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