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RESPONSE TO 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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We appreciate the comments from Theodorakis (1) in response to our findings of reduced glucagon-like peptide 1 (GLP-1) release in prediabetes, screen-detected type 2 diabetes, and obesity (2). Theodorakis suggests that participants with screen-detected diabetes in the ADDITION-PRO study may have had long-standing diabetes, which could then explain why findings on GLP-1 release in participants with type 2 diabetes in the ADDITION-PRO study and the Baltimore Longitudinal Study of Aging (BLSA) point in different directions.

The ADDITION-PRO study performed in 2009–2011 was originally designed to quantify diabetes progression rates, examine early markers of micro- and macrovascular diabetes complications, and understand the related mechanisms in a large group of individuals at low to high risk of developing type 2 diabetes (3). The cohort for the ADDITION-PRO study was nested within the ADDITION-DK study—a population-based stepwise screening program in Danish general practice performed in 2001–2006 (4). All individuals invited for the ADDITION-PRO examination had low diabetes risk, normal glucose tolerance, or prediabetes in 2001–2006. Participants diagnosed with diabetes since the examination in 2001–2006 or people reporting the use of antidiabetic medication at the examination in 2009–2011 were excluded from the analysis (2). At the 2009–2011 examination, 163 individuals without known diabetes were diagnosed with screen-detected diabetes. Of these, 76 had normal glucose tolerance, 80 had prediabetes, and 7 scored low on a questionnaire for diabetes risk in 2001–2006. Therefore, it is unlikely that participants diagnosed with screen-detected diabetes at the examination in 2009–2011 had long-standing diabetes, and they were not receiving antidiabetic treatment prior to their study attendance. In fact, the 163 participants with screen-detected diabetes in the ADDITION-PRO study had on average a "healthier" phenotype than the 17 patients with type 2 diabetes who participated in the BLSA, in which increased release of GLP-1 was found (5). All 17 individuals with diabetes in the BLSA had both diabetic fasting and 2-h glucose values, and they had an average HbA_{1c} level of 7.0% (5). In the ADDITION-PRO study (2), 82 were diagnosed with diabetes by fasting glucose only, 43 by 2-h glucose only, and 38 by both fasting and 2-h glucose concentrations, and the average HbA_{1c} level was 6.1%. Diagnosis of diabetes by only the fasting or the 2-h glucose criterion is associated with a less severe phenotype than diagnosis by both criteria (6), underscoring that individuals with screen-detected diabetes in the ADDITION-PRO study were diagnosed at an early stage of their disease.

We agree with Theodorakis that differences in the duration and severity of type 2 diabetes are likely to

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contribute to the diverse results reported in the literature, but in general both parameters are associated with further decreases in GLP-1 secretion (7) as also mentioned by Theodorakis (1). The detailed knowledge of the ADDITION-PRO participants' glucose tolerance status 5–8 years before they entered the clinical examination in 2009–2011 shows convincingly that individuals with screen-detected diabetes in the ADDITION-PRO study did not have long-standing diabetes. Accordingly, our findings demonstrate reduced GLP-1 release early in the pathogenesis of type 2 diabetes.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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