RESPONSE TO COMMENT ON RETNAKARAN ET AL.

Liraglutide and the Preservation of Pancreatic β-Cell Function in Early Type 2 Diabetes: The LIBRA Trial. Diabetes Care 2014;37:3270–3278

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We thank Arnolds and Sawicki (1) for their interest in our recent publication describing the LIraglutide and β-cell RepAir (LIBRA) Trial (2). The LIBRA Trial was a double-blind, randomized, placebo-controlled trial that was designed to objectively evaluate the effect of liraglutide on the preservation of β-cell function over 1 year in patients with early type 2 diabetes (T2DM), following the initial amelioration of glucotoxicity-induced dysfunction with 4 weeks of prerandomization intensive insulin therapy (IIT). The primary outcome of baseline-adjusted β-cell function at 48 weeks (measured by Insulin Secretion-Sensitivity Index-2 [ISSI-2]) was significantly higher in the liraglutide arm compared with the placebo arm, but this effect did not persist after a 2-week washout. Thus, this trial demonstrated that liraglutide can provide robust enhancement of β-cell function that is sustained over 48 weeks in early T2DM but is lost with cessation of therapy.

Arnolds and Sawicki (1) suggest that prerandomization IIT did not improve β-cell function and that the observed effect of liraglutide on β-cell function can be attributed to the effects of the medication on weight and glycemic control. First, it should be noted that the impact of IIT on improving β-cell function in the prerandomization phase of this trial has been previously reported (3,4), consistent with a recent meta-analysis demonstrating the beneficial effect of short-term IIT on endogenous insulin secretion when administered early in the course of T2DM (5). Although the improvement in β-cell function that it induced was modest in overall magnitude, prerandomization IIT achieved the intended goals of ameliorating glucotoxicity (as shown in Fig. 1 of ref. 3) and reducing glycemia in both arms (as shown in Fig. 2*A* of ref. 2), thereby yielding a level playing field upon which to objectively evaluate the potential β-cell-protective capacity of liraglutide versus placebo. Second, it is important to recognize that, after adjustment for BMI, baseline-adjusted ISSI-2 at 48 weeks remained significantly higher in the liraglutide arm as compared with the placebo arm (341.0 ± 28.0 vs. 227.6 ± 28.6, $P = 0.007$). Similarly, upon adjustment for HbA_{1c}, baseline-adjusted ISSI-2 again remained higher in the liraglutide group (320.8 ± 22.6 vs. 248.7 ± 23.0, $P = 0.03$). These data thus suggest that the beneficial effect of liraglutide on β-cell function in the LIBRA Trial cannot be solely attributed to its effects on weight and glycemic control.

Overall, the findings from the LIBRA Trial indicate that, after prerandomization IIT to eliminate glucotoxicity-induced β-cell dysfunction, liraglutide can further enhance endogenous insulin secretion and maintain this effect over 48 weeks. However, as noted in the original reporting of the trial (2), we believe that the fact that the marked enhancement of β-cell function induced by liraglutide was completely lost within 2 weeks of stopping the medication suggests that the underlying pathology driving β-cell deterioration in T2DM was not reversed by this therapy.

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