Reply to the comment of Wilbrink et al. on Retrospective analysis of liraglutide and basal insulin combination therapy in Japanese type 2 diabetes: The association between remaining β-cell function and the achievement of the HbA1c target 1 year after init

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We would like to thank Wilbrink et al. for their interest and comments on our recent article regarding the glycated hemoglobin (HbA1c)-lowering effect of glucagon-like peptide-1 receptor agonist liraglutide with basal insulin among Japanese individuals with type 2 diabetes.

We have reported that the HbA1c-lowering effects of liraglutide/basal insulin combination rely on remaining β-cell function, and that the cut-off value of the C-peptide immunoreactivity index, a β-cell function-related index frequently used in Japanese clinical settings, is 1.103 for the achievement of HbA1c < 7.0% at 54 weeks after initiating the liraglutide/basal insulin combination. In our study, we found that changes in HbA1c were not affected by type 2 diabetes duration, unlike the Wilbrink et al. study (Figure 1b). This discrepancy might be due to several reasons. First, we studied patients receiving liraglutide/basal insulin combination in replacement of multiple daily injection insulin therapy or basal insulin-supported oral therapy, whereas Wilbrink et al. studied those receiving liraglutide in replacement of insulin therapy. We previously showed that discontinuation of liraglutide as a result of hyperglycemia after switching from insulin is affected by remaining β-cell function and type 2 diabetes duration. In addition, we also reported that the HbA1c-lowering effects of liraglutide monotherapy and sulfonylurea combination rely on remaining β-cell function and type 2 diabetes duration.

Importantly, the C-peptide immunoreactivity index cut-off value for HbA1c < 7.0% achievement by liraglutide monotherapy and sulfonylurea combination was higher than that of liraglutide/basal combination (1.86 and 1.10, respectively)². It is widely accepted that β-cell function progressively declines over time in type 2 diabetes patients, making it difficult to obtain appropriate glycemic control without insulin use. It is possible that basal insulin co-administration compensated for the decline in β-cell function associated with longer type 2 diabetes duration in our study. Indeed, it was shown that the addition of basal insulin significantly improved HbA1c in individuals inadequately controlled by liraglutide. Second, the discrepancy between our study and the Wilbrink et al. study might be due to ethnic difference in type 2 diabetes pathophysiology. Type 2 diabetes in East Asian patients is characterized primarily by non-obesity and β-cell dysfunction, unlike type 2 diabetes in Caucasian patients, which is characterized by obesity and insulin resistance. As impaired β-cell function is observed even in the early stage of type 2 diabetes in East Asian patients, type 2 diabetes duration might have less significance in predicting the HbA1c-lowering effects of liraglutide. Third, the discrepancy might be due to limited sample size (the Usui study on liraglutide/basal insulin, n = 38; the Usui study on liraglutide monotherapy or sulfonylurea combination, n = 88; and the Wilbrink et al. study, n = 69). Dependence of HbA1c-lowering effects of liraglutide/basal insulin combination on type 2 diabetes duration awaits further investigation by studies with larger sample sizes. Nevertheless, it is conceivable that liraglutide exerts greater HbA1c-lowering effects in the early stage of type 2 diabetes when ample β-cell function remains, and that addition of basal insulin or other antidiabetic drugs is required when β-cell function becomes substantially reduced.
Figure 1 | Changes of glycated hemoglobin (HbA1c) in Japanese patients with type 2 diabetes receiving (a) liraglutide monotherapy or sulfonylureas (SU) combination and (b) liraglutide/basal insulin combination. The patients were subdivided into two groups by medians of type 2 diabetes duration: (a) 10 years and (b) 16 years. Blue, those with type 2 diabetes duration below the median: (a) n = 37 and (b) n = 18; and red, those with type 2 diabetes duration with the median or above: (a) n = 51 and (b) n = 19. Time-course curves were analyzed by mixed-effects models including group, time, and the interaction of group and time; and the P-values are shown. *P < 0.05 (vs patients with the median or above) by the Mann–Whitney U-test. The statistical analysis was carried out using SPSS Statistics 24 software (IBM Corp., Armonk, New York, USA). Each value represents the mean ± standard error of the mean.

DISCLOSURE

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