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 initiation

We would like to thank Wilbrink et al.\(^1\) 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\(^2\). 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 supports the decline in insulin is affected by remaining β-cell function and type 2 diabetes duration\(^3\). 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 (Figure 1a) in a study in which 74% of the study patients had been taking insulin before initiating liraglutide\(^4\). 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)\(^5,6\). 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\(^5,6\). 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\(^2\). Indeed, it was shown that the addition of basal insulin significantly improved HbA1c in individuals inadequately controlled by liraglutide\(^7\). 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\(^8\). 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.

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REFERENCES

1. Wilbrink FJ, Mudde AH, Mulder AH, et al. Disease duration as an indicator of the efficacy of liraglutide in patients...


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