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LETTER TO THE EDITOR

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 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)[2,4]. 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.

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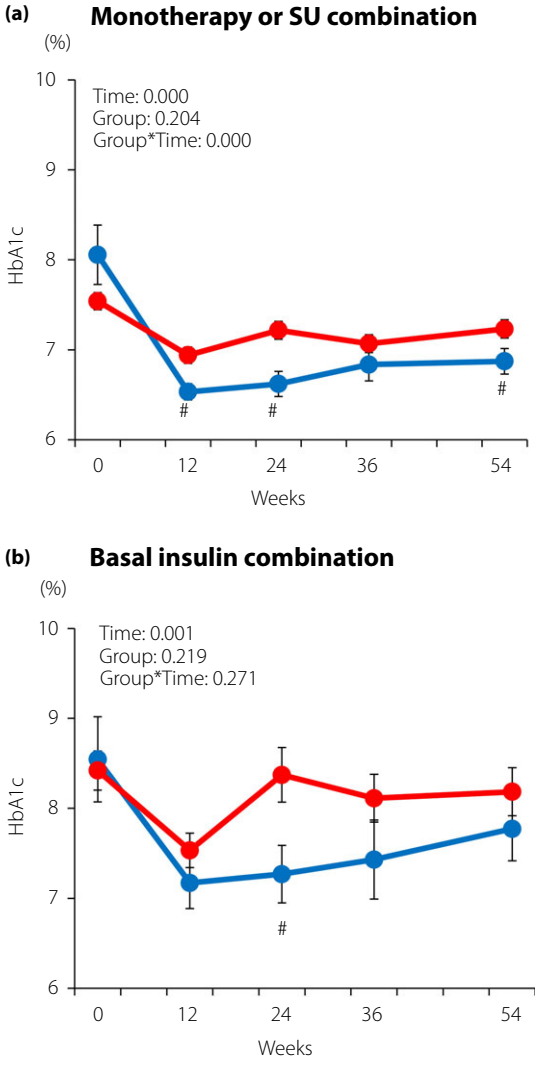

Figure 1 | Changes of glycated hemoglobin (HbA1c) in Japanese patients with type 2 diabetes receiving (a) liraglutide monotherapy or sulfonylureas (SU) combination and (b) liraglutide/basal insulin combination. The patients were subdivided into two groups by medians of type 2 diabetes duration: (a) 10 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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