**A commentary on the “consensus statement” regarding the use of BIAsp30**

A consensus statement by experts on intensifying insulin therapy using biphasic insulin aspart-30 (BIAsp30) was recently made public. This statement is a valuable contribution in that it presents simplified criteria for the first time. However, diabetes mellitus is diverse in its pathophysiological features. It therefore seems essential for physicians to select an optimum method of intensifying insulin therapy tailored to the individual patient’s condition, rather than adhering uncritically to the use of BIAsp30 recommended in the consensus statement. (J Diabetes Invest, doi: 10.1111/j.2040-1124.2010.00017.x, 2010)

Unnikrishnan et al. recently issued a consensus statement on intensification of insulin therapy using biphasic insulin aspart-30 (BIAsp30). In the past, numerous sets of guidelines for the treatment of diabetes mellitus have been made public, but there seems to be no set of guidelines published to date that provide detailed ways of using individual drugs. In view of the fact that the start of intensification of insulin therapy tends to be delayed, an approach that promotes the introduction of this therapy based on evidence supported by concrete data seems to have clinical value.

This consensus statement proposes algorithms for the following two actions related to the use of insulin preparations, on the basis of the results from past large-scale clinical studies on BIAsp30:

- (i) switching from long-acting (basal) insulin injection therapy to intensified therapy with BIAsp30; and (ii) increasing the frequency of BIAsp30 treatment from once or twice daily to twice or three times daily.

(i) If patients receiving long-acting (basal) insulin therapy aiming to supplement basal insulin secretion fail to achieve a HbA1c reduction of below 8.0% or if the fasting plasma glucose level (FPG) of such patients is in the normal range (4–6 mmol/L) although HbA1c is in the 7–8% range, the therapy is switched to twice daily BIAsp30 therapy (insulin doses, before breakfast:before supper = 50:50), while keeping the daily insulin dosage unchanged. In both of these cases, switching to BIAsp30 is aimed at correcting postprandial hyperglycemia, probably attributable to a shortage of insulin after meals when only long-acting insulin is used. In contrast, in patients whose HbA1c is in the 7–8% and FPG >6 mmol/L, the dose of long-acting insulin is increased until the FPG is lowered to 6 mmol/L. (ii) If patients receiving BIAsp30 once or twice daily have a FPG in the normal range (4–6 mmol/L) and HbA1c >7.0%, the frequency of BIAsp30 treatment is increased to twice or three times daily so that postprandial hyperglycemia can be alleviated. If patients receiving BIAsp30 once or twice daily have a FPG >6 mmol/L, the BIAsp30 dose is increased in steps. If the latter patients develop hypoglycemia before FPG normalization, the frequency of insulin treatment is increased to twice or three times daily because the insulin dose cannot be simply increased from that level. When the frequency of insulin treatment is increased from once to twice daily, the daily insulin dosage remains unchanged, but it is divided into two doses at a 50:50 ratio given before breakfast and before supper. If the frequency of insulin treatment is increased from twice to three times daily, the consensus agreement recommends initially adding a dose of 2–6 U or 10% of the daily dosage before lunch. If the frequency of BIAsp30 treatment is increased from once to twice daily, the additional dose of BIAsp30 at suppertime is expected to suppress blood glucose elevation after supper and to lower the FPG through its long-lasting activity. If the frequency is increased from twice to three times daily, the long-acting insulin administered at a higher daily dose is expected to suppress elevation of the blood glucose level all day and night.

The importance of blood glucose control has been pointed out for many years. The importance of adequate control is not confined to the fasting blood glucose level. Many studies have shown that postprandial hyperglycemia can induce glucotoxicity and is thus involved in the progression of diabetes mellitus, and that postprandial hyperglycemia causes vascular endothelial dysfunction, elevating the onset risk of major vascular complications and retinopathy. Despite these findings, the introduction of insulin therapy to patients with type 2 diabetes mellitus tends to be delayed, and there are many cases where insulin therapy is not started and chronic hyperglycemia is left uncontrolled, even after the development of secondary sulfonylurea failure. When insulin therapy is started, the once daily injection of a long-acting soluble insulin analog preparation is often used. However, because long-acting insulin preparations were originally designed for use as a means of supplementation for the shortage of basal insulin secretion, the use of this kind of insulin preparation cannot be expected to correct the shortage of postprandial additional insulin secretion, one of the characteristics of type 2 diabetes mellitus. As a result, sufficient blood glucose control is not achieved in many patients treated with such a preparation. According to the report from the IMPROVE study using BIAsp30, the...
introduction of insulin therapy with BIAsd30 or switching from other insulin preparations to BIAsp30 resulted in improved blood glucose control, accompanied by a reduction in the incidence of severe hypoglycemia and improvement in the satisfaction of patients with treatment⁴⁵. We might therefore state that an early start of intensified insulin therapy to prevent postprandial hyperglycemia is a desirable treatment approach from the viewpoint of improving the prognosis of patients, and that the consensus statement by Unnikrishnan et al. is valuable because it presents simple criteria that every clinician can refer to during routine clinical practice.

However, in view of the diversity of the pathophysiological features of diabetes mellitus, the proposed algorithms do not appear to be adequately capable of dealing with such variation. Although the biphasic insulin analog mixture is advantageous in terms of its capability to replenish both basal insulin secretion and postprandial additional insulin secretion through one injection, the ratio of the required amount of basal insulin secretion to that of additional postprandial insulin secretion varies among individual patients and, for this reason, there is a limitation in the approach of selecting a treatment method relying on BIAsp30 alone. The author has also encountered cases where the adequate suppression of postprandial hyperglycemia was not achieved by BIAsp30, or where hypoglycemia developed early in the morning or before supper after a BIAsp30 dose increase. To achieve the adequate control of postprandial hyperglycemia and reduce the incidence of hypoglycemia during fasting, it is desirable to select a method of treatment tailored to the condition of a given patient (e.g. elevating the percentage of rapid-acting type insulin used). At present, clinically available biphasic mixed insulin analog preparations are confined to BIAsp30 and two mixed insulin lispro preparations (containing 25 and 50% rapid-acting type insulin, respectively). BIAsp50 and BIAsp70 are expected to enable treatment with a biphasic mixed insulin analog preparation in more patients⁶. As stated above, the pathophysiological features of diabetic patients are diverse, and it seems essential to select an optimal regimen of intensive insulin therapy for each individual patient when insulin injection is used for treatment.

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