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Insulin regimen in type 2 Diabetes Mellitus patients with poor glycemic control

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Type 2 diabetes mellitus is a progressive pathological status in which the function of beta cells declines and the glycated hemo-globin level over time. The maintenance of nearly normal glycemic levels is the goal for each patient, reducing the risk of diabetic complications. The diabetic control is difficult over time and often requires addition of insulin to the oral antidiabetic drugs, such as metformin, sulfonylureas, and thiazolidinediones. However, many patients do not reach targets for glycated hemoglobin with conventional insulin regimens, and there is concern regarding hypoglycemia and weight gain. Large-scale, direct comparisons of various regimens of insulin analogues in combination with antidiabetic oral drugs are lacking.

Treating to Target in Type 2 Diabetes (4-T) is a 3-year, multicenter, open-label, randomized, controlled clinical trial. The trial compared the efficacy and safety of adding three insulin regimens to the treatment of 708 patients with type 2 diabetes (aged 61.7±9.8 and a median duration of disease 9 years) who had suboptimal glycemic control while receiving maximally tolerated doses of metformin and sulfonylurea. Patients with history of thiazolidinediones or gross diabetic complications were excluded. All patients had suboptimal glycemic control (a glycated hemoglobin level of 7.0 to 10.0%). The patients were randomized into three groups, one with biphasic insulin analogue aspart[1], one with prandial aspart and the last with basal insulin detemir[2] on top of oral medication.

The primary outcome was the glycated hemoglobin level at 1 year.

The maximal reduction in the mean glycated hemoglobin level occurred by 24 weeks and then remained stable. At 1 year, mean glycated hemoglobin levels were similar in the biphasic group (7.3%) and the prandial group (7.2%) ((P=0.08) but higher in the basal group (7.6%, P<0.001 for both comparisons). The respective proportions of patients with a glycated hemoglobin level of 6.5% or less were 17.0%, 23.9%, and 8.1%; respective mean numbers of hypoglycemic events per patient per year were 5.7, 12.0, and 2.3; and respective mean weight gains were 4.7 kg, 5.7 kg, and 1.9 kg. Rates of adverse events were similar among the three groups. ❑

CONCLUSION

A single analogue-insulin formulation added to metformin and sulfonylurea resulted in a glycated hemoglobin level of 6.5% or less in a minority of patients at 1 year. The addition of biphasic or prandial insulin reduced levels more than the addition of basal insulin detemir. The good control of the disease in the prandial group was balanced by a higher risks of hypoglycemia and by a higher weight gain. The treatment of a type 2 diabetic patient should be individualized and has to include the most suitable regimen of insulin on top of antidiabetic medication in order to achieve a proper control. ❑

[1]insulin aspart – DNA recombinant, short acting insulin
[2]insulin detemir – DNA recombinant, long acting insulin

Comment on the paper:
Holman RR, Thorne KI, et al for 4-T Study Group – Addition of Biphasic, Prandial, or Basal Insulin to Oral Therapy in Type 2 Diabetes, www.nejm.org September 21, 2007 (10.1056/NEJMoa075392)