

This Week's Question:

Comes from this weeks newsletter Item#2

Combining rosiglitazone, metformin, and insulin aspart improved glucose metabolism in obese type 2 diabetic patients compared with mixed insulin alone, according to the results of an open-label, randomized trial published in the December issue of *Diabetes Care*.

Which of the following would not be a benefit of the above triple therapy?

1. Improved peripheral insulin sensitivity
2. Improved hepatic insulin sensitivity
3. Improved glycemic control
4. Improved weight control

Triple therapy addresses three pathophysiological components of type 2 diabetes: reduced insulin secretion and insulin resistance in skeletal muscle and in the liver. In triple therapy, insulin aspart (a rapid-acting insulin analog) is used to address reduced insulin secretion, metformin is used to improve hepatic insulin sensitivity, and rosiglitazone is used to improve peripheral insulin sensitivity. The authors hypothesize that compared with insulin therapy alone, triple therapy can produce better outcomes in HbA_{1c} levels, insulin dosage required, number of hypoglycemic episodes, and diurnal profiles of glucose.

Type 2 diabetes is caused by reduced insulin secretion and insulin resistance in skeletal muscle and liver," write Mikael Kjær Poulsen, MD, from Odense University Hospital in Denmark, and colleagues. "There has been a tradition for many years to use only one antidiabetic drug at a time, and most patients are still treated with either insulin secretagogues or insulin alone. However, these drugs have only a minor effect on cardiovascular events and mortality, whereas metformin, which improves insulin sensitivity, is able to reduce the risk of myocardial infarction and reduce the mortality rate."

For six months, 16 obese type 2 diabetic outpatients receiving human NPH or MIX (regular + NPH) insulin twice daily either received triple therapy or continued their NPH or MIX insulin twice daily. Triple therapy consisted of insulin aspart, a rapid-acting insulin analog, at meals; metformin, which improves hepatic insulin sensitivity; and rosiglitazone, which improves peripheral insulin sensitivity. Algorithms directed adjustment of insulin doses in both groups.

In the triple therapy group, mean HbA_{1c} decreased from 8.8% to 6.8% ($P < .01$) without occurrence of severe hypoglycemic events, and insulin sensitivity improved in both skeletal muscle and liver. Postprandial hyperglycemia was infrequent. The diurnal profile of serum insulin was characterized by fast and high peaks without the need to increase insulin dose. Triple therapy was not associated with significant weight gain or impairment in plasma lipids, blood pressure, or safety parameters other than hemoglobin.

Although the insulin dose was increased by 50% in the control group, there was no change in HbA_{1c} levels, 24-hour blood glucose levels, or insulin sensitivity.

"These results strongly indicate that normalization of the three major pathophysiological defects of type 2 diabetic subjects, namely peripheral insulin resistance, hepatic insulin resistance, and reduced insulin response following meals, can significantly improve glucose metabolism," the authors write. "Triple therapy seems a promising treatment for hyperglycemia in type 2 diabetic subjects, but long-term studies are necessary. However, if these results are confirmed, diabetes complications may be dramatically reduced."

Novo Nordisk provided insulin aspart, GlaxoSmithKline provided rosiglitazone, and Merck provided metformin. Novo Nordisk and GlaxoSmithKline provided honoraria for speaking engagements to three of the study authors. The Clinical Institute, University of Southern Denmark; Bernard Rasmussen and wife Meta Rasmussen's foundation, Overlægerodets Legatudvalg; Den Almindelige Danske Lægeforening's science foundation; Novo Nordisk, Denmark; and GlaxoSmithKline, Denmark, supported this study.

Pearls for Practice

- ? Triple therapy addresses both reduction in insulin secretion and insulin resistance (liver and peripheral) in obese patients with insulin-requiring type 2 diabetes.
- ? Triple therapy over six months results in improved HbA_{1c} levels, diurnal glucose profile, and insulin sensitivity than therapy with insulin alone, with no increase in hypoglycemic episodes. Long-term trials are pending.