The evidence for insulin lispro

In their critique of the review article by Anuradha L. Puttagunta and Ellen L. Toth[1] on insulin lispro therapy, James McCormack and Ken Bassett[2] have inaccurately interpreted the existing clinical data on our product. They write, "Postprandial blood glucose levels were lower in the insulin lispro groups, but the clinical significance of this difference must be questioned, given that it did not translate into a reduction in the incidence of hypoglycemic episodes or levels of hemoglobin A_{1c}." In fact, Anderson and colleagues[3] showed a significant difference between insulin lispro and regular insulin therapy in the mean number of hypoglycemic episodes (3.18 v. 3.43 episodes per 30 days per patient, $p < 0.02$). Overnight hypoglycemia was reduced significantly as well (0.47 episodes per 30 days per patient for insulin lispro v. 0.73 for regular insulin, $p < 0.001$).

Zinman and colleagues[4] also demonstrated a significant reduction in hypoglycemia with insulin lispro compared with baseline (12.7 episodes per 30 days at baseline v. 8.6 after 3 months of insulin lispro, $p = 0.035$). This was associated with improved levels of hemoglobin A_{1c}. A recent meta-analysis by Brunelle and colleagues[5] also clearly demonstrated a 30% reduction in severe hypoglycemia with insulin lispro compared with regular insulin (3.3% v. 4.4%, $p = 0.024$). Insulin lispro is the first insulin product capable of improving the hemoglobin A_{1c} levels with fewer hypoglycemic episodes, rather than more, as occurred in the Diabetes Control and Complications trial.[6]

The issue of the effect of insulin lispro therapy on hemoglobin A_{1c} also needs clarification. McCormack and Bassett quote the meta-analysis by Davey and colleagues[7] as evidence that there is no significant difference between insulin lispro and regular insulin in this respect. However, they fail to point out that Davey and associates alluded to the fact that the studies evaluated for the meta-analysis were not necessarily designed to demonstrate significant changes in hemoglobin A_{1c} levels. More recent studies, which were specifically designed to examine the effect of insulin lispro on hemoglobin A_{1c} and which directed proper attention toward adjusting the basal insulin and meal plan in conjunction with insulin lispro therapy, have demonstrated the ability of insulin lispro to provide for a lower hemoglobin A_{1c} level with fewer hypoglycemic episodes.[8-11]

Finally, a number of the abstracts that McCormack and Bassett dismiss as not providing sufficient detail have now, in fact, been published as full papers.[5,8]

Numerous studies of insulin lispro therapy have demonstrated lower postprandial glycemic excursions, fewer hypoglycemic episodes overall, and fewer severe and overnight hypoglycemic episodes. More recent reports have demonstrated lower hemoglobin A_{1c} levels without an increased risk of hypoglycemia.

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Competing interests: Dr. Grossman has financial interests in Eli Lilly Canada Inc.

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[The authors respond:]

The table included as part of our critique[1] of the review article on insulin lispro therapy by Anuradha L. Puttagunta and Ellen L. Toth[2] does not contain any inaccuracies. In their Table 2, Anderson and colleagues[3] reported the risk of hypoglycemia at end point as virtually identical for regular insulin and insulin lispro therapy: 2.79 and 2.67 episodes per 30 days for regular insulin and insulin lispro respectively ($p = 0.31$). In the text, they did report that the mean hypoglycemic rates, which were inexplicably different from the end-point hypoglycemic rates, were different between the 2 treatment groups. However, the absolute difference in hypoglycemic episodes between the 2 groups was almost identical to the absolute differences between the groups at baseline. Our concern with this study is not with the number of hypoglycemic episodes reported, but with its validity. It used an open study design to determine the frequency of subjectively reported mild hypoglycemic episodes.

Blinded trials are needed to assess hypoglycemic episodes as well as more objective end points such as hemoglobin A_{1c} levels. Blinding requires giving both forms of insulin at the same time before meals. Zinman and colleagues[4] have shown that blinded trials are safe and therefore ethical. They did *not* find

a statistically significant difference in rates of hypoglycemic episodes between the regular insulin and insulin lispro groups. It is difficult to extrapolate from their findings because patients used continuous insulin infusion technology and intensive assessment.

The strength of a meta-analysis depends on the strength of the trials on which it is based. The primary problem in the insulin lispro literature lies in determining the strength of the individual trials. The meta-analysis by Davey and colleagues, for example, included 8 unpublished trials involving 2500 patients and 3 published trials involving 30 patients.[5] An additional problem is that the published trials are methodologically weak. The meta-analysis by Brunelle et al,[6] which at the time was not available to us or to Puttagunta and Toth when they wrote their article, was based on open trials. Accepting or rejecting its conclusions, which showed a decrease in the number of severe hypoglycemic episodes (1.3% absolute difference) in favour of insulin lispro but no benefit for insulin lispro with respect to hemoglobin A_{1c}, must await full publication of valid, randomized blinded studies.

Loren Grossman lists 4 additional references to defend his statement that "more recent studies … have demonstrated the ability of insulin lispro to provide for a lower hemoglobin A_{1c} level with fewer hypoglycemic episodes." However, the studies by Ebeling and colleagues[7] and Ronnemaa and colleagues[8] rank among case series, the methodologically weakest form of evidence. They are trials of switching from regular insulin to insulin lispro therapy. Ebeling and colleagues showed an 0.8% reduction in hemoglobin A_{1c} levels and no difference in hypoglycemic events. Ronnemaa and colleagues found no difference in hemoglobin A_{1c} or hypoglycemic events until they looked at a subset of patients. As Ebeling and colleagues correctly state, "it is not possible to estimate how much of the improvement in glycemia and HbA_{1c} was due to insulin lispro … or how much is due to the intensive attention the patients were given during the study." Grossman's last 2 references are to abstracts, and 1 of these describes research involving only 6 patients.

It is important to reiterate that our original letter was meant to criticize *CMAJ*'s decision to publish Puttagunta and Toth's article as much as it was intended to question the value of insulin lispro itself. The article was neither systematic in its data gathering nor scientific in its appraisal of the evidence. Systematic review and critical appraisal methodology is now widely known and vigorously endorsed by medical educators and health care administrators. Publishing methodologically weak systematic review articles such as this one significantly undermines these collective efforts. Although selective reporting of data and references to trials that are not well designed can often appear to be "evidence based," closer examination often reveals that the emperor has no clothes.

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Adjudicating ethics in research

Miriam Shuchman[1] indicates that a national body should have been available to investigate, evaluate and adjudicate the issues raised by the controversy surrounding Dr. Nancy Olivieri and The Hospital for Sick Children.

The National Council on Ethics in Human Research is a multidisciplinary organization with a mandate to advance the protection and promotion of the well-being of human participants in research and to foster high ethical standards for the conduct of research involving humans. The council has the responsibility to assist research ethics boards in interpreting and implementing the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (1998). The council has established an ongoing mechanism to assess the functions of research ethics boards

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