Hypoglycemia due to Serum-complexed Insulin in a Patient with Diabetes Mellitus

The recent article by Albert and Popp[1] highlighted the potential for insulin antibodies to cause problems other than clinical allergy and overt insulin resistance. The case reported involved a hyperlabile insulin-dependent diabetic patient in whom presumed antibodies with heterogeneous binding affinities radically altered insulin pharmacokinetics with resultant extremes of hyper- and hypoglycemia. The origins of the clinical syndrome in that patient were presumably related to the use of impure insulins on a chronic basis with resultant antigenic stimulation and, ultimately, production of insulin antibodies. Simply switching the patient to a purified insulin, even of the beef species, resulted in gratifying clinical amelioration of the patient's hyperlabile state. In terms of using human insulin, the authors expressed the opinion that no particular advantage would be derived; however, one would anticipate that human insulin, being less antigenic than beef insulin, would result in radically lower antibody titers with enhanced long-term clinical stability. The authors' rationale for such a negative attitude toward human insulin was unclear. The reference to the different effects experienced with pork and beef insulins could be explained simply by the fact that on the morning when the pork insulin was administered, the fasting blood sugar was at least 200 mg/dl higher with no documentation of ketones, which may have contributed further to a variable degree of insulin resistance on that day. Furthermore, no direct comparisons were made with human insulin, either of the biosynthetic or semisynthetic nature. Empirically, we have been switching all hyperlabile type I diabetic patients to purified insulins in the hope of reducing antibody titers, and avoiding the potential problems documented in the study by Albert and Popp. The problems with control we have experienced in these patients have not been as intense as those of the patient of Albert and Popp, but essentially have been episodes of hypo- and hyperglycemia that appeared unrelated to diet, physical activity, and changes in insulin dosage and insulin administration sites.

It appears plausible that many type I diabetic individuals may exist with problems similar to those of the patient documented by Albert and Popp, which manifest as episodes of hitherto unexplained modest hyper- and hypoglycemia. We feel that insulin antibodies may not behave just as simple carrier proteins[2] with a stable equilibrium between the free and bound states, but may behave in a more erratic fashion with either the antibody-bound insulin exerting independent insulin action or perhaps resulting in erratic release of free insulin from the antibodies.[3] In view of the current drive toward more intensified insulin therapy and better normalization of blood sugars, we feel that antibody-related problems of diabetic control may be unmasked more frequently as clinical awareness increases. Hopefully, the more widespread use of purified, less antigenic insulins will result in lower overall antibody titers and, hopefully, the removal of one further variable in the multiplicity involved in the overall control of type I diabetic individuals.

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REFERENCES

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Hypoglycemia due to Serum-complexed Insulin: A Reply

We hope that our article (Diabetes Care 1984; 7:285–90) might be interpreted at several levels. At the first level, we were faced with a difficult clinical management situation, that of a patient with alternating hyper- and hypoglycemia. Drs. Sheehan and Sisam make valid clinical suggestions. They are correct that the patient had been on "impure" insulins since she first developed diabetes 13 yr ago. We also anticipated that porcine and human insulin would be less antigenic than bovine insulin. At the time that the subject was evaluated, human insulin was not commercially available and we tried a tolbutamide tolerance test to stimulate endogenous insulin release. There was no evidence of ketosis on any of the 3 days of insulin testing. We were also surprised that there was a biologic response to bovine insulin, with lesser responses to porcine and endogenous insulins. We did not prospectively evaluate the serum to document the titers of circulating antibodies to the three species of insulin in order to document a change in titer with switching to more purified insulins. Again at a clinical level, the patient continues to do extremely well on the purified bovine preparation. Switching this patient to human insulin has been considered, but has been logistically difficult due to physical and social problems.

A second explanation for her improved clinical control may be due to the switch from intermediate-acting insulin to regular insulin. In fact, the regular insulin seems to behave as an intermediate-acting insulin due to serum binding.

At a second level we hoped that the article might stimulate further thought regarding the biologic role of bound insulin. As researchers in the field of diabetes we are perfectly willing to accept a double standard. Insulin may be complexed to