Recurrent insulin resistance

B. A. LEATHERDALE
B.Sc., M.R.C.P.

D. A. INGRAM
B.Sc., M.B. B.S.

K. DIXON*
M.A., Ph.D.

*Department of Diabetes and Endocrinology, Dudley Road Hospital, Birmingham, and
Clinical Chemistry Department, General Hospital, Birmingham

Summary

The patient described developed 2 separate episodes of insulin resistance and on each occasion daily administration of soluble insulin in a daily dose of 980 units failed to achieve satisfactory control. Both episodes responded to steroid therapy. The maximum binding capacity of the serum for insulin was measured on each occasion; in the first episode it was grossly elevated whereas the second time the level was unremarkable. She is currently free of diabetic complications and satisfactorily controlled on a sulphonylurea and diet.

Introduction

Insulin resistance has been arbitrarily defined as the requirement of more than 200 units of insulin daily for a period greater than 48 hr, in the absence of ketoacidosis, infection or associated endocrinological disorder. It is rare; a large series from the Joslin clinic (Boston, U.S.A.) suggests a frequency of less than one in 1000 diabetic out-patients. The resistant state tends to be self-limiting, the majority of cases remitting within a few months.

A case is now reported where two entirely separate episodes of insulin resistance developed, a situation which, it is claimed, has not been recorded before. The first episode was associated with the presence of a high serum maximum binding capacity (MBC) for insulin but during the second episode the MBC was not significantly raised.

Case report

A 47-year-old West Indian woman was diagnosed as diabetic when she was 36 years old and had been initially controlled with a 150-g carbohydrate diet and tolbutamide 500 mg thrice daily; she was gravida 11, para 10, with 4 perinatal deaths and 4 infants with birth weights > 4.5 kg. Two pregnancies

had followed the diagnosis of diabetes. The first ended in a miscarriage (when she was 40 years old) at 2 months' gestation and, during her last pregnancy when she was 41 years old (April 1970) she was admitted for stabilization and controlled on lente insulin 20 u./day. Spontaneous rupture of the membranes occurred at approximately 32 weeks' gestation and she then required soluble insulin 24 u. in the morning and 18 u. in the evening until premature delivery at approximately 33 weeks. She was discharged on 1 August, 1970, taking 28 u. of lente insulin/day but was re-admitted on 19 August in diabetic precoma. Her diabetes was difficult to control. She initially improved with rehydration and insulin in doses of 160-200 u./day, but control deteriorated subsequently and by 3 September she was poorly controlled despite 400-600 u./day of insulin. The introduction of neutral insulin injection had little effect on her insulin dose or control and on 8 September she was taking 980 u. of neutral insulin injection daily, with blood sugars ranging between 10-30 mmol/l, but she was not ketotic. Control was eventually achieved and the dose of neutral insulin injection reduced to 60 u. thrice daily and she was started on prednisolone 5 mg thrice daily (3 October 1970). Insulin requirements fell dramatically over the next week and she was discharged on 9 October 1970, well controlled on neutral insulin injection 36 u. in the morning and 24 u. in the evening. Her prednisolone was quickly withdrawn and she remained stable on approximately 50-60 u. of neutral insulin injection daily until April 1975.

Between April and December 1975 her requirements of neutral insulin injection rose insidiously and control deteriorated with a loss of 7 kg in weight. By January 1976 she was taking 192 u. of soluble insulin thrice daily but remained poorly controlled and she was re-admitted for stabilization. Control could not be achieved, even on 980 u. daily

and again prednisolone 60 mg/day was introduced. The effect of steroids was dramatic and within 3 days control was regained and she was discharged on soluble insulin 36 u. in the morning and 28 u. in the evening with prednisolone 20 mg thrice daily. Steroids were gradually withdrawn and stopped in July 1976. Control was reasonably good and her weight increased dramatically to 88 kg from approximately 65 kg in January 1976.

In August 1977 she was re-admitted to hospital and given chlorpropamide. Subsequently her diabetes has been as well controlled on chlorpropamide 500 mg daily and diet, as it had previously been on insulin.

Discussion

It is well recognized that insulin resistance can either follow an insidious increase in insulin requirement, usually over several months or be ushered in more rapidly after an episode of ketoacidosis (Shipp *et al.*, 1965; Malins, 1968). The present patient demonstrated both presentations on separate occasions, the first phase occurring soon after beginning treatment with insulin and the second some 5 years later. Resistance has been reported in association with many systemic diseases, notably haemochromatosis, liver disease, acanthosis nigricans, blood dyscrasias and reticuloses (Shipp *et al.*, 1965; Malins, 1968) which may only become

clinically apparent after an interval of several years from diagnosis of the insulin-resistant state (Shipp *et al.*, 1965; Malins, 1968). The present patient was thoroughly investigated to find such a cause for her insulin resistance and none has been found.

Apart from the rare cases reported in which antibodies to the insulin receptor site have been demonstrated (Kahn *et al.*, 1976) such patients usually have a MBC for insulin of greater than 10 u./l (K. Dixon, personal communication) and this observation can be grossly elevated (Berson and Yallow, 1960). The MBC is the amount of insulin which will be bound by the serum when it is saturated with insulin. Serum from patients who have never formed antibodies to insulin have a MBC of zero. The first episode in the patient was associated with a very grossly elevated MBC of 114 u./l but in the second episode a modest figure of 3.4 u./l was initially obtained and levels fell progressively during steroid therapy (Fig. 1). It therefore seems likely that during the initial episode the MBC was related to the insulin-resistant state but the second episode cannot be explained on this basis. The lower MBC in the second episode correlates with the known lower antigenicity of porcine insulin which had been administered since the initial episode.

It has always been difficult to understand why

FIG. 1. Variation in insulin requirements and serum maximum binding capacity for insulin during resistant phases and remission periods. — Insulin dose, x · · · x maximum binding capacity, ■ steroid therapy.

such patients recover from their resistant state despite continued antigenic stimulation in the form of exogenous insulin administration. The second episode in the patient raises the possibility that the role of circulating antibodies in the genesis of this syndrome has been exaggerated. The importance of the insulin-receptor site in insulin-resistant states such as obesity has recently been emphasized (Olefsky, 1976). It seems possible that reduction or blockage of hepatic receptor sites rather than induction of binding antibodies could have caused the second episode of resistance and the dramatic response to steroids might indicate that these agents in some way modify the insulin receptor on the hepatocyte and render circulating insulin more effective.

It is noteworthy that despite the high levels of

insulin-binding antibodies this patient showed no evidence of diabetic complications.

References

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