



THREE PATIENTS WITH IMMUNE MEDIATED COMPLICATIONS ASSOCIATED WITH SUBCUTANEOUS INSULIN TREATMENT

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Background and clinical presentation of patients:

Immune mediated complications associated with s.c. insulin therapy are rare conditions since human insulin is in general use. Nevertheless, if it occurs, a stepwise diagnostic approach is essential for differential diagnosis facilitating optimal therapy. In this study, based on three s.c. insulin treated patients, we introduce such a diagnostic approach and suggest differential therapeutic regimens to deal with high titres of insulin antibodies and/or severe skin reactions resulting in poor metabolic control in all of the subjects.

Pat. 1: Type 1 D.m. for 5 years, female, 41 years old, s.c. insulin therapy (Protaphane, Semilente, Actrapid/ later Novo rapid) since the time of diagnosis. No preserved c-peptide fasting/post-p.: <0.1 ng/ml. HbA1c 7%, no dermal reactions, but frequent and unexplained hypoglycemic episodes (once/twice daily and during the night)

Pat. 2: Type 2 D.m. for 18 years, female, aged 78 years, s.c. insulin therapy (Depot H/later Insuman comp 25) since 2 years. Extremely high c-peptide plateau levels fasting/post-p.: 9.7 vs. 9.8 ng/ml. Severe skin reaction immediately after s.c. injection of s.c. insulin, poor metabolic control, HbA1c 8.6%

Pat. 3: D.m. following partial pancreatectomy, male, 58 years old, s.c. insulin therapy (Berlinsulin 30/70) since 6 months. Elevated c-peptide plateau levels fasting/post-p.: 4.1 vs. 4.5 ng/ml, severe skin reactions immediately after s.c. insulin, poor metabolic control, HbA1c 9.3%

Methods: Beside routine clinical/laboratory testing including c-peptide, HbA1c etc. we performed the following immunological evaluation:

A. Intradermal skin testing to assess allergic reactions of the immediate and/or late type. Positive control (Histamin), negative-control (Aqua dest.), galenic components (Insuman Testlösungen, Aventis) and different insulin preparations (Aventis, Novo, Lilly)

B. Quantification of insulin specific IgG (normal: <0.03 mU/ml, in-house-RIA) and IgE antibodies (normal: RAST 0, CAP-system, Pharmacia)

C. To determine the clinical relevance of these antibodies we analyzed the time dependent binding/dissociation curves of the insulin/antibody complexes in an ex vivo/in vitro assay (in-house-assay with ¹²⁵J-Insulin, controls: 20 Type 1 diabetic, insulin treated subjects without a history of allergic reactions and well controlled diabetes. The bound/ free ratio in this group is approx. 3-5% at time point 0, no delayed dissociation over time, **Figure 3**).

Results: In **Pat. 2** we identified Protamine as the challenging antigen for the local skin reaction, **Figure 1**. **Pat. 3** generated insulin specific IgE antibodies exhibiting a severe/immediate local skin reaction against all insulin preparations used (**Figure 2**).

Patient 2 (Figure 1)
Intradermal skin testing
Pos.-control – Histamine
Neg.-control – Aqua dest.
#8,9: Testreag. – Protamine
(+ reaction)



Patient 3 (Figure 2)
Intradermal skin testing
Pos.-control – Histamine
Neg.-control – Aqua dest.
#3-10: Diff. insulins
(+ reaction)



In all of the patients we found high levels of insulin specific IgG abs (**Pat 1:** 0.37mU/ml, **Pat. 2:** 0.27 mU/ml, **Pat. 3:** 0.43 mU/ml, normal: <0.03 mU/ml), binding approximately 60-70% of the insulin with delayed dissociation as shown in **Figure 3**.

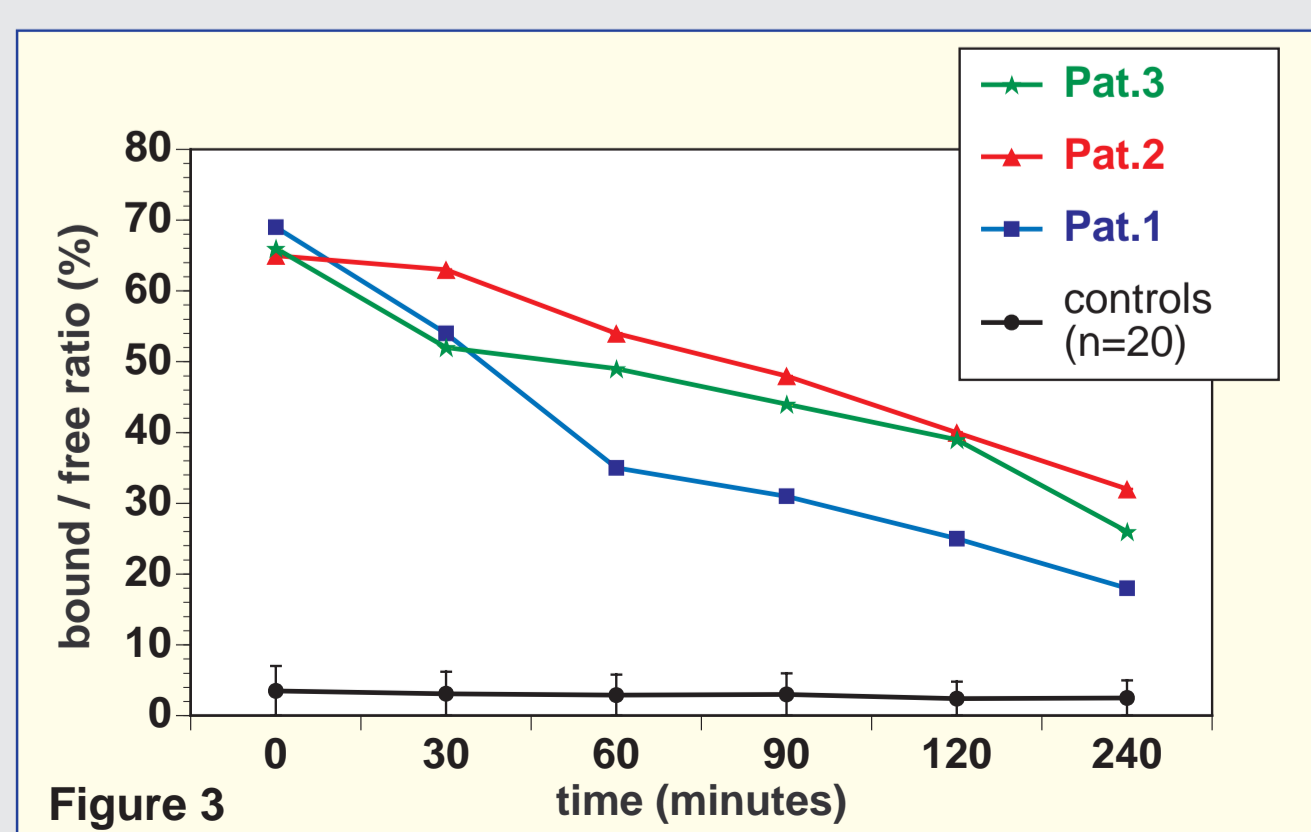


Figure 3

Therapeutic approach and Conclusions

For **Pat. 1** we suggested CSII with a human insulin analogue in order to adjust the insulin delivery to steady state conditions. The HbA1c decreased to 6.1%, and the frequency of hypoglycemic episodes was significantly lowered to 1-2 per month.

The high plateau levels of fasting/post-p c-peptide levels in **Pat. 2 and 3** are potentially induced through a relative insulin shortage because of the large amount of antibody-bound/inactivated insulin. **Pat. 2** was set on prandial insulin therapy only (analogue, no protamine). The HbA1c was lowered to 7.6 %, skin reactions were no longer noted. **Pat. 3** was set on max. OAD therapy without insulin. The HbA1c fell to 7.8%, in the absence of skin reactions.

The proposed combined approach allows differential diagnosis and adjusted therapy of different forms of immune mediated complications associated with s.c. insulin therapy.