Glycaemic control: evaluations of HbA1c as a risk factor and the effects of modern insulins in clinical practice

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This thesis is based on the following papers:

I. Österbrand M, Fahlén M, Odén A, Eliasson B. A method to predict the metabolic effects of changes in insulin treatment in subgroups of a large population based patient cohort. European Journal of Epidemiology. 2007;22:151-15.

II. Lind M, Fahlén M, Happich M, Odén A, Eliasson B. The effect of insulin lispro on glycemic control in a large patient cohort. Diabetes Technology & Therapeutics. 2009;11:51-6.

III. Lind M, Odén A, Fahlén M, Eliasson B. A systematic review of HbA1c variables used in the study of diabetic complications. Diabetes and Metabolic Syndrome: Clinical Research and Reviews. 2008;2: 282-293.

IV. Lind M, Odén A, Fahlén M, Eliasson B. The true value of HbA1c as a predictor of diabetic complications: simulations of HbA1c variables. PLoS ONE. 2009;4:e4412.

V. Lind M, Odén A, Fahlén M, Eliasson B. A methodological study of the temporal relationship between HbA1c and retinopathy in the Diabetes Control and Complications Trial (DCCT). 2009. *Submitted.*

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Abstract

One of the ultimate goals of diabetes care is to minimise diabetic complications. When evaluating insulins it is important to understand what extent of improvements in glycaemic control is clinically relevant in preventing diabetic complications. We have thus both studied the effects on glycaemic control of the most commonly used insulins and the relations between glycaemic control and diabetic complications.

In analyses electronical tracking of patient record systems and data from the landmark study Diabetes Control and Complications Trial (DCCT) were used. Research and statistical models were developed to estimate time-dependent effects between HbA1c and diabetic complications.

Patients receiving insulin glargine in clinical practice have decreased on average 0.18% in HbA1c compared to patients continuing with NPH insulin. Lean men had the greatest reductions in HbA1c. In corresponding analyses of insulin lispro reductions of HbA1c by 0.19% were achieved compared to patients continuing with regular insulin. Patients with high HbA1c experienced the greatest reductions in HbA1c.

When relating HbA1c to diabetic complications we introduced the term HbA1c-variable describing different weightings and combinations of HbA1c values. In a systematic review we found that the baseline value was most common to use in studies of HbA1c and diabetic complications, but a mean value of many HbA1c values had greater predictive ability. By simulations we showed that HbA1c-variables comprising time-dependent effects of HbA1c could have 100% greater predictive power than a mean value. In the DCCT we could confirm these results and describe the temporal relationship between HbA1c and retinopathy. Over 6 years an HbA1c-level of 8% instead of 7% predicted 92% greater risk of retinopathy when time-dependent effects were considered instead of 50% with a mean value. HbA1c values 2.4 years ago had the largest deleterious effects on current risk of retinopathy and historical values up to 5 years ago were more harmful than present values. The current salutory effect of a constant lower level of HbA1c increased steadily with time since both present and previous values reduce the current risk of retinopathy. When lowering HbA1c from 9% to 7% 274 patients had to be treated during the first 3 years after diagnosis, but only 2 patients during the period 9-12 years to prevent retinopathy. With time also relatively small HbA1c changes of 0.3% showed a low NNTof 13.

In conclusion good glycemic control is more important than earlier recognised in preventing retinopathy. Insulin lispro and insulin glargine improve glycaemic control in clinical practice and the reductions obtained in HbA1c are clinically relevant. In medicine time-dependent effects of treatments and risk factors should be regarded in epidemiologic and clinical trials to understand the magnitude of the effects. Electronical tracking of data in clinical research and quality improvement is more efficient than manual collection, extensive information is retrieved and costs are reduced substantially.

*Key word*s: HbA1c, glargine,lispro, time, retinopathy, clinical practice, electronical tracking, record system

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