Beta-cell function and metabolic control in Latent Autoimmune Diabetes in Adults (LADA) with early insulin vs conventional treatment: A three-year follow-up

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Key terms: LADA, insulin, beta-cell-function, C-peptide, HbA1c

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Abstract

Objectives: The optimal treatment of LADA is not established. We explored whether early insulin treatment, which has shown beneficial effects in rodents and in human pilot studies, resulted in better preservation of beta-cell function, or metabolic control, compared to conventional treatment.

Subjects and methods: Glucagon-stimulated C-peptide and HbA1c were evaluated at baseline and after 12, 24 and 36 months in 37 patients recently diagnosed with diabetes, aged ≥30 yrs, non-insulin-requiring and GADAb and/or ICA positive. Twenty patients received early insulin and 17 conventional treatment (diet ± OHA, metformin, some and/or SU) and insulin when necessary.

Results: Level of metabolic control, HbA1c, was preserved in the early insulin treated, while it significantly deteriorated in the conventionally treated. There was no significant difference between the groups in C-peptide after 12, 24 or 36 months, or in the decline of C-peptide. Only baseline C-peptide predicted a C-peptide of ≥0.5 nmol/l at 36 months. Gender, BMI, antibody titres or HbA1c did not influence levels of C-peptide or Hba1c at baseline or end-of-study, or the decline in C-peptide. Among the diet±OHA-treated 5/17 (30%) developed insulin-dependency during follow-up. No major hypoglycaemic events occurred.

Conclusions: Early insulin treatment in LADA lead to better preservation of metabolic control and was safe. Superior preservation of C-peptide could not be significantly demonstrated. Only baseline level of C-peptide significantly influenced C-peptide level after 3 years. Further studies exploring the best treatment in LADA are warranted.
Introduction

Most adults with autoimmune diabetes not insulin-requiring at diagnosis become so within 3-6 yrs (1, 2). The optimal treatment for this the second largest group of patients with diabetes is still unknown (3-7). Adult patients with autoimmune diabetes usually have larger remaining beta-cell mass at diagnosis and many develop beta-cell destruction more slowly. LADA is therefore a suitable group for evaluating new therapies in autoimmune diabetes and may also serve as model for intervention in classical type 1 diabetes (3, 4, 6-9).

The incidence of autoimmune diabetes is about equal in almost all age groups (10, 11). Abrupt onset, often with ketoacidosis, is most frequent during childhood, a more modest onset is more frequent in adolescents and younger adults, and among adults and elders a slowly progressive onset, termed LADA, is frequent (3, 4, 11, 12). Classical type 1 diabetes and LADA patients often have normal C-peptide levels at diagnosis, but further progressive decline occurs after onset, and insulin dependency occurs almost inevitably (3, 4, 8, 9, 13).

Most trials in early type 1 diabetes have been performed in children, where remaining beta-cell mass is limited, and short term evaluation of intervention may be difficult also due to not infrequently occurring remission periods (14, 15). No therapy has yet been demonstrated to promote long term insulin independency (3, 5, 7, 16). Rodent studies have demonstrated potential positive effects of insulin treatment (17, 18). A pilot study of small doses of insulin vs sulfonylurea (SU) to ten ICA- positive patients with slowly progressive beta-cell failure favoured insulin for preservation of C-peptide (19). C-peptide is the outcome measure of choice of beta-cell function in trials of autoimmune diabetes (20). Even modest preservation of beta-cell function has been demonstrated to have positive effects on the frequency of
hypoglycaemic events, and on the prevalence of retinopathy (21). Connection between glycemic control and development of complications is well established (21-23).

**Objective**

To investigate the effect of early insulin treatment of LADA patients, during three years, on residual beta-cell function and metabolic control, compared to a group initially treated with diet and/or oral hypoglycaemic agents (OHA).

**Subjects and methods**

Adults, aged ≥30 yrs, diagnosed with diabetes in Lund and Kronoberg counties in southern Sweden, non-insulin-requiring at diagnosis and positive to at least one of GADAAb and/or ICA were eligible for participation. Two thirds had to be excluded due to mental conditions or severe physical illness, but also unwillingness to risk early start of insulin injections. The majority of the patients were randomized into two groups, in blocks of eight, by pre-prepared closed envelopes kept at the two hospital policlinics, but complete strict randomization was not possible, since some patients refused randomization to possible insulin treatment before it was unavoidable. They were referred to the control group. There were 20 patients in the intervention group (I), treated with insulin from baseline, starting with 2-6 units intermediate-acting insulin at night; and 17 patients in the control group (C) who received regular treatment with diet ± oral hypoglycaemic agents (OHA), mostly metformin, and some SU (5/17; 30%). For both groups, goals for glucose levels were in accordance with general guidelines (FPG 4.5-7, preprandial PG 5-7, postprandial PG 6-9 mmol/l). Decisions to increase treatment in
doses, number of doses, addition of OHAs or insulin, were at the discretion of the treating physician. If two doses/day of intermediate-acting or mix-insulin was not satisfactory doses of direct or rapid acting insulin before meals was added, resulting in 1-4 doses/day. Patients were either treated at the hospital policlinics, or continued at their health care centre.

Residual beta-cell function was evaluated by glucagon-stimulated C-peptide. Glucagon-stimulation-tests were performed at baseline and after 12, 24 and 36 months during annual policlinic visits at the two research clinics. After over-night fast C-peptide was determined before and 6 minutes after intravenous injection of 1 mg Glucagon (24). C-peptide was analyzed by commercial radioimmunoassay (MD315, Euro-Diagnostica AB, Sweden), total variation (sum of intra-and interassay variation) 7%, reference range 0.25-1.0 nmol/l, detection limit 0.13 nmol/l. C-peptide level to reflect a preserved normal beta-cell function was arbitrarily set at 0.5 nmol/l. ICA were analysed with immunofluorescence assay, with detection limit 9 JDF-U, sensitivity 100%, specificity 88%. GADab were analysed with radioimmuno-precipitation with lower reference limit at an index of 0.08, corresponding to 21 WHO-U/ml, sensitivity 70%, specificity 100%. IA-2A were analysed with enzyme-linked immunosorbent assay and all analyses standardized according to the Diabetes Antibody Standardization Program (25, 26). Metabolic control was assessed by HbA1c (Mono-S), and values were converted to DCCT-standard (27).

Regarding the metabolic syndrome, complete information was available only regarding BMI and prevalence of hypertension, defined as blood pressure >140/80 mm Hg at the baseline visit, or taking antihypertensive medication.

All subjects provided informed consent. The study was approved by The Ethical Committee of Lund University. The study is registered in ClinicalTrials.gov Identifier: NCT01109927.
Statistical methods

Analyses were carried out according to intention-to-treat. For comparisons between groups Student’s T-test, Chi-square or Fisher’s exact test, and the Mann-Whitney U-test, were performed where appropriate. C-peptide and HbA1c at baseline and after 12, 24, and 36 months were analyzed with repeated-measures-ANOVA using time as covariate; for three group analyses ANOVA, with Bonferroni correction where appropriate. Risk factors and relations were analyzed in several models with simple, multiple, linear and logistic regressions (forward stepwise, Wald). All tests were two-sided, p <0.05 was considered significant. SPSS software, version 17.0 (Chicago, Ill, USA) was used.

Results

For baseline characteristics of the groups see table 1. There were no significant gender differences in the whole study, except that in the control group there were only men with hypertension, (p 0.03). Most subjects were overweight since both the I and C groups had mean BMI \( \geq 27 \text{ kg/m}^2 \). Median duration of diabetes at inclusion in the study was 5.0 (quartiles 3.0-9.0) months. In both groups 90% of the patients, 18/20 in I and 15/17 in C, completed 36 months of follow-up. Four patients withdrew consent. Among the conventionally treated (C) 30% (5/17) started insulin treatment due to clinical necessity within 6-6-12-18-24-30 months.

Beta-cell-function

For levels of glucagon-stimulated C-peptide see table 2, and figure 1. C-peptide levels were unchanged for four patients, increased by mean 0.73(±0.5) nmol/l for six, and declined for all
others during 36 months. Mean glucagon-stimulated C-peptide decreased significantly in both
groups during the 36 months (p <0.0001). There was a significant time trend for the decrease
in C-peptide of 0.17 nmol/l/year, (p 0.03), over 36 months without any significant difference
between the groups. In a repeated-measures-ANOVA with time as covariate, that analyses the
changes in C-peptide over time with the levels at baseline taken into account, no differences
could be found regarding mean stimulated C-peptide at any time point, although with the
Mann-Whitney U-test the difference in C-peptide at baseline was significant, p 0.03. There
were large variations in C-peptide levels between different individuals, at all time points,
within both the groups, (p <0.0001), explaining all the variation between them, Figure 1 A+B.

Cp0 explained 43% of level of Cp36, $R^2 0.43$ (p <0.0001). Furthermore, age was the only
other factor that had a weak and non-significant influence on Cp36, explaining about 5% of
Cp36, $R^2 0.049$ (p 0.2). The influence of age was eliminated when included in a multiple
regression model. Gender, baseline or end-of-study values of BMI, titres of GADA or ICA,
HbA1c or diabetes duration before study start did not influence C-peptide at end-of-study.

There was no significant difference in the proportion of patients with a Cp36 $\geq 0.5$ nmol/l. it
was 86% (13/15) in C, and 61% (11/18) in I (p= 0.13).

The odds ratio (OR) for having a Cp36 $\geq 0.5$ nmol/l was 2.4 for every increase in Cp0 with
0.10 nmol/l (p 0.02), and 1.06 for each increase in baseline age by one year, (p= 0.03). If
correcting for Cp0 and age, the two factors found to have any influence on Cp36, the insulin
treated had a non-significant OR of 2.5 (0.04-184) of having a Cp36 of $\geq 0.5$ nmol/l.

The results for levels of fasting C-peptide, (FCP) when comparing the two treatment groups
(data not shown) were in accordance with the described results of stimulated C-peptide.

**Metabolic control**
Among the controls the level of HbA1c had increased significantly at 36 months from 7.0 (±1.3)% to 7.5 (±1.5)%, (p 0.006) (Figure 2). In the intervention group there was no significant difference between HbA1c at baseline, 7.3 (±1.3)%, and after 36 months, 7.2 (±0.7)% (p 0.6) (Figure 2). For levels of HbA1c at baseline and during follow-up see Table 2 and Figure 2. The differences between the groups in absolute levels of HbA1c were not significant either at baseline or after 12, 24 or 36 months. The levels of HbA1c were not influenced by age, gender, BMI, antibody prevalences or titres, or C-peptide levels.

**Autoimmunity**

At baseline prevalences of GADAb were 94%, ICA 67%, 72% had both antibodies, 22% GADAb only, and 6% only ICA, with no significant differences between the two treatment groups. Of the 32 patients for which IA-2A status was known 7 (22%) were positive, all of them also positive to GADAb and all but one was positive to ICA, meaning that 75% of all were positive to at least two antibodies.

At baseline mean indexes of GADAb were 0.78 (±0.39) in I, in C 0.78 (±0.48) (ns), and mean ICA titres were 29.4 (±40) in I, 72.4 (±119) JDF-U in C (ns). At baseline there were no significant differences in the prevalences of either of the three antibodies between the two treatment groups, or between genders, different ages, duration of diabetes before study start, or levels of BMI or HbA1c. Neither were there any significant differences between the groups in titres of GADAb or ICA after 12, 24 or 36 months. The titres of GADab or ICA were not related to patient age, gender, BMI, diabetes duration, treatment or HbA1c at baseline or during follow-up. C-peptide at baseline or 36 months was not influenced by baseline titre of GADAb, ICA or IA-2A.

**Adverse events**
No episodes of major hypoglycemia were reported for any of the patients, and only a few minor ones.

Mean weight at baseline was 77.4 (±14.5, range 57.8-110) kg in group I, and 83.0 (±17.8, range 50.8-117) kg in group C (ns); at end-of-study 79.3 (±12.4, 57.7-101) kg in I, 82.3 (±14.8, range 50.4-115) kg in C (ns). Mean weight change during the study was 2.5 (±4.8, range -8.8- +9.3) kg in I; -1.0 (±10.5, range -27.3-+16.4) kg in C (ns).

**Three group analysis and ever - vs never -insulin-treated**

For three groups, those treated with insulin from baseline, those never treated with insulin, and those who were originally treated with diet ± OHA, but had to start insulin treatment during the study, the influences of age, BMI, HbA1c, diabetes duration before study start, or antibody titres, were analyzed, with no significant findings except for the influence of Cp0 on Cp36. The tests for all the relevant parameters were also carried out with the 37 patients divided in groups of ever vs never (during the study) insulin-treated, again with no significant results (p 0.12-0.87), apart from the significant influence of Cp0 on Cp36 (p<0.0001).

**Discussion**

Few prospective intervention studies have been conducted in LADA patients and there is still no general agreement on the best treatment aimed to preserve beta-cell function (5-7, 16). There has not been any general consensus definition of LADA which complicates comparisons and pooling of results. The most common denominators are adult age, positivity to at least one pancreatic autoantibody, and non-insulin-dependency at diagnosis (4). Age, BMI, duration of diabetes and of insulin-independency, which antibodies are analysed,
GADAb titres, and expression of the essential outcome variable C-peptide vary (2, 4, 5, 28-30). A Cochrane review also noted the heterogeneity between studies, and the conclusion about early insulin treatment was uncertain (5). Our study included patients aged ≥30 yrs, non-insulin-dependent at the times of diagnosis and inclusion, and positive to at least one pancreatic autoantibody, for 75% two antibodies, thereby fulfilling the main criteria for LADA (4). The results of the study indicated that none of the baseline parameters, except initial C-peptide level, significantly influenced outcome, eliminating the importance of several criteria in comparisons with other studies. In other studies patients aged >65 yrs have often been excluded, but LADA exists also in these older age groups (11).

The decline in residual beta-cell function was progressive for the majority of our LADA patients, as is usual in autoimmune diabetes (4, 8, 13, 16). We observed great variation in the rates and magnitudes of beta-cell loss between patients, and between different time periods during the study, with no consistent patterns. Mechanisms such as more step-wise losses due to for instance partial remissions might explain this (15). The decline in C-peptide was irrespective of age, gender, BMI, antibody titres, HbA1c or treatment modality. The lack of influence of BMI, age, diabetes duration and baseline HbA1c on disease progression was also seen in a non-interventional observation study of LADA that followed 13 Ab-positive patients by stimulated C-peptide for 2 years (16).

Similarly to UKPDS we found no association between GADAb levels and disease progress (31), in contrast to observational studies that described this (30, 32). We could in a number of regression analyses not define any other factor, besides Cp0, that significantly influenced the level of Cp36. The significance of initial C-peptide level was also demonstrated in a large Swedish study of new-onset 15-34-year-olds, and in the Tokyo intervention study (28, 33). The length of our study may explain that some patients with initially higher levels of C-
peptide, overrepresented in the control group, by 36 months had not yet lost enough beta-cell function to be clinically insulin-dependent. Some antibody-positive patients have been described to take up to 12 years to become insulin-dependent, but practically all eventually did (34).

A significant beneficial effect of early insulin treatment on the preservation of beta-cell function could not be demonstrated, but level of HbA1c after 36 months was better preserved in the insulin-treated, in keeping with observations by Chaillous et al in a smaller group of antibody-positive patients (16). Incidentally, the shape of the curve of the development of HbA1c levels over time for the conventionally treated group in our study had a likeness to that observed in the UKPDS (35).

Our study, as most prospective intervention studies of LADA, was not large. The Tokyo study with 60 patients, found a preference for insulin treatment vs SU, possibly due to the differences in treatment, but longer duration of diabetes, up to five years without insulin before inclusion, rendering a selection of patients with better endogenous insulin production from the start, would have excluded those who progressed earlier to insulin dependence, so the trial population differed from ours (28). Baseline level of C-peptide was an important independent predictor of the ability to preserve a sufficient amount of C-peptide over time, just as in our study.

Many reports end with a general recommendation of insulin treatment in LADA, but the evidence has not been compelling, as concluded by the 2007 Cochrane review, which scrutinized seven insulin intervention studies in LADA, two insulin-vs-SU, the rest insulin-alone vs different combinations of insulin+OHA (5). UKPDS recorded HbA1c, weight and treatment, randomized to insulin vs SU, and found that 60% of the SU-treated were insulin-dependent after two years (36). One conclusion was that SU might promote insulin
dependency and apart from not recommending SU the Cochrane review found no preference
for any special type of treatment to the LADA group (5). In our study after three years 65% of
the conventionally treated patients were not yet treated with insulin. In contrast to both
UKPDS and the Tokyo Study, only 30% of our control patients were treated with SU which
could be of importance for beta-cell function. In one study, of 54 patients in four groups, the
insulin-treated, all with low FCP, ≤0.3 nmol, received either insulin-alone, or combined with
rosiglitazone (RGZ), and the OHA-treated, all with FCP >0.3 nmol/l, received SU or RGZ
(29). The results indicated that all who received RGZ better preserved their beta-cell function.

Further considerations

To our knowledge the present is the first prospective controlled European intervention study
of treatment in LADA. Differences in defining the LADA population regarding age, diabetes
duration before start of intervention, antibody prevalences and GADAb titres, BMI, and, not
least, baseline levels of C-peptide, if available, have contributed to difficulties in interpreting
and comparing results of the few existing LADA intervention studies (4, 5, 28, 29, 37). In this
study none of those factors, except baseline level of C-peptide, significantly affected outcome.
The similar findings also seen in trials of classical type 1 diabetes and of prevention of
autoimmune diabetes in high risk individuals, substantiates the observation of the influence of
initial level of C-peptide on outcome level (38, 39).

We found a significantly better preservation of metabolic control in the early insulin treated.
We also saw a non-significant OR favouring insulin treatment for preservation of beta-cell
function, indicating the possibility that a larger study population and/or a longer period of
follow-up might have demonstrated significant preference for early insulin treatment also
regarding beta-cell function.
Conclusions

This study indicated that early insulin treatment of LADA patients lead to better preservation of level metabolic control, and that it was safe and well tolerated. It could not significantly confirm better preservation of beta-cell function. The decline in C-peptide was progressive irrespective of age, gender, BMI, HbA1c levels, and antibody titres. Only baseline level of C-peptide significantly influenced C-peptide level after three years. Further studies exploring the best treatment of LADA patients are warranted.

Disclosure

M Landin-Olsson has received a part-time professorship sponsored by Novo Nordisk Scandinavia. The other authors have no dualities of interest to declare.

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<th>Control Group</th>
<th>p-value</th>
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<tr>
<td>Age (yrs)</td>
<td>54.1 (± 14.9) [30-80]</td>
<td>51.0 (± 14.3) [30-75]</td>
<td>57.8 (± 15.1) [31 – 80]</td>
<td>ns</td>
</tr>
<tr>
<td>Gender Men (%)</td>
<td>51.4</td>
<td>45.0</td>
<td>58.8</td>
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</tr>
<tr>
<td>Diabetes duration (months)</td>
<td>5.0 [1 - 24]</td>
<td>6.0 [1.5 - 24]</td>
<td>5.0 [1 - 22]</td>
<td>ns</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.8 (± 6.2) [19.4 - 49.5]</td>
<td>27.0 (± 6.9) [19.4 - 49.5]</td>
<td>28.7 (± 5.3) [22.0 - 42.2]</td>
<td>ns</td>
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<tr>
<td>C-peptide (nmol/l, stim)</td>
<td>1.45 (± 0.83) [0.29 – 3.4]</td>
<td>1.2 (± 0.73) [0.29 - 3.0]</td>
<td>1.7 (± 0.86) [0.65-3.4]</td>
<td>p 0.03</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.2 (± 1.3) [5.2 - 10.1]</td>
<td>7.3 (± 1.3) [5.6 - 10.1]</td>
<td>7.0 (± 1.3) [5.2-9.5]</td>
<td>ns</td>
</tr>
<tr>
<td>Titre GADA (index, ref &lt; 0.08)</td>
<td>0.78 (± 0.43) [0.6-1.6]</td>
<td>0.78 (± 0.39) [0.06 -1.6]</td>
<td>0.78 (± 0.48) [0.12-1.6]</td>
<td>ns</td>
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<tr>
<td>Titre ICA</td>
<td>50.2 (± 89) [0.0-449]</td>
<td>29.4 (±40.5)</td>
<td>72.4 (±118)</td>
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<tr>
<td>Hypertension (%)</td>
<td>39.4</td>
<td>41.2</td>
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<td>BMI &gt; 25 kg/m² (%)</td>
<td>42.0</td>
<td>43.5</td>
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<tr>
<td>Hypertension + BMI &gt;25 kg/m² (%)</td>
<td>32.4</td>
<td>29.4</td>
<td>37.5</td>
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Table 1  Baseline characteristics of the LADA groups. Values are mean (± SD) [range], except duration, which is median.
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<th></th>
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<th>Control group</th>
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<tr>
<td><strong>Mean ± SD</strong></td>
<td>Min</td>
<td>Max</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>C-peptide baseline</td>
<td>1.45 (±0.8)</td>
<td>0.29</td>
<td>3.4</td>
</tr>
<tr>
<td>C-peptide 12 months</td>
<td>1.35 (±0.9)</td>
<td>0.00</td>
<td>3.4</td>
</tr>
<tr>
<td>C-peptide 24 months</td>
<td>1.17 (±0.8)</td>
<td>0.00</td>
<td>3.6</td>
</tr>
<tr>
<td>C-peptide 36 months</td>
<td>0.99 (±0.8)</td>
<td>0.00</td>
<td>3.6</td>
</tr>
<tr>
<td>HbA1c baseline</td>
<td>7.2 (±1.3)</td>
<td>5.2</td>
<td>10.1</td>
</tr>
<tr>
<td>HbA1c 12 months</td>
<td>6.9 (±1.2)</td>
<td>5.2</td>
<td>10.9</td>
</tr>
<tr>
<td>HbA1c 24 months</td>
<td>7.1 (±1.2)</td>
<td>5.1</td>
<td>9.3</td>
</tr>
<tr>
<td>HbA1c 36 months</td>
<td>7.3 (±1.1)</td>
<td>5.3</td>
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Table 2. Levels of glucagon-stimulated C-peptide (nmol/l) and HbA1c (% DCCT-standard), for all participants, and for the groups.
Figure 1 A
Figure 1 B
Figure 2.