Comparison of Insulin Aspart vs. Regular Human Insulin with or without Insulin Detemir Concerning Adipozytokines and Metabolic Effects in Patients with Type 2 Diabetes Mellitus

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Key words
- adipocytokines
- insulin
- type 2 diabetes mellitus

Abstract

Background: In type 2 diabetes mellitus, treatment with insulin is initiated when HbA1c is reduced inadequately with oral antidiabetic drugs or incretin mimetics. Whether insulin analogues vs. regular human insulin have favorable effects in terms of efficacy and metabolism is under discussion.

Patients: 29 patients with type 2 diabetes mellitus (19 males, 10 females) with a mean age 59±11(mean±SD) years (range 24–75) and treated with oral drugs for at least 6 months and a HbA1c >7.0% were included in an open, randomised, prospective, controlled, multicenter parallel-group study over a period of 24 months.

Methods: 11 patients were randomized in the regular human insulin-group (RHI-group) and 18 patients in the insulin aspart group (IA-group). Insulin aspart or regular human insulin should be treated to <140 mg/dl postprandial and insulin detemir should be treated to <110 mg/dl in the morning (fasting) after a previous dose titration of insulin aspart or regular human insulin over 6 months of treatment. Adiponectin, HbA1c, fasting plasma glucose, BMI, triglycerides and cholesterol levels were determined every 3 months.

Results: 7/11 of the RHI-group received additional insulin detemir and 13/18 of the IA-group. HbA1c levels decreased significantly in both groups (8.7±1.6 to 7.2±0.9 in the RHI-group ($p<0.05$) vs. 8.7±1.6 to7.3±0.9 in the IA-group ($p<0.05$)) without significant difference between the groups. No significant changes were seen between the 2 groups during the 24 months period in terms of BMI, fasting plasma glucose, lipids. Adiponectin serum levels decreased over the time without difference between the groups (7.9±4.0 to 5.0±2.0 in the RHI-group ($p<0.03$) vs. 7.3±3.4 to 4.8±2.8 in the IA-group ($p<0.0001$)). During the first 9 months, the insulin dosage to reach the postprandial blood glucose <140 mg/dl, were significantly lower in the IA-group, but approached the following the RHI-group without significant changes after 24 months.

Conclusion: After stopping oral antidiabetic drugs in type 2 diabetes mellitus, insulin aspart in comparison to human regular insulin decreased effectively HbA1c levels without significant difference. Moreover, insulin aspart in comparison to human regular insulin does not have any substantial benefits concerning metabolic effects and adipocytokines in type 2 diabetes mellitus over a 24 months treatment period.

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Bibliography
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Introduction

Patients with type 2 diabetes have an increased risk of cardiovascular complications like myocardial infarction, arrhythmias and stroke [1]. This may be due to the concomitant hypertension, dyslipoproteinaemia and obesity and the inadequate glucose control [2]. The aim of any diabetes treatment is to normalise HbA1c levels and especially to reduce postprandial glucose levels [3–6]. When HbA1c levels remain elevated under oral antidiabetic drugs, insulin therapy is recommended. Whether insulin analogues are superior to regular human insulin is still under discussion [7]. Beside the advantage of immediately injection before meal with insulin analogues, normalization of glucose levels can be achieved with lower insulin dosage in comparison to human regular insulin [8]. And lower insulin dosages may correlate with insulin sensitivity.

Adiponectin is one of several adipocytokines and correlates with insulin sensitivity [9–11]. Therefore, treatment with insulin analogues may have beneficial effects on insulin sensitivity and higher adiponectin levels [6].

Table 1 Baseline characteristics of 29 patients with type 2 diabetes mellitus under treatment with oral antidiabetic drugs.

human regular insulin	insulin aspart	
number	11	18
sex (male/female)	8/3	11/7
age [yr]	60 ± 9	58 ± 12
BMI [kg/m²]	32.8 ± 4.8	31.5 ± 5.8
waist circumf. [cm]	112 ± 7	107 ± 16
HbA1c [%]	8.7 ± 1.6	8.7 ± 1.6
adiponectin [µg/ml]	7.9 ± 4.0	7.3 ± 3.4
pro-insulin [pmol/l]	26.6 ± 19.2	19.4 ± 16.4
triglycerides [mg/dl]	241 ± 210	273 ± 272
total-cholesterol [mg/dl]	191 ± 29	209 ± 50
LDL-cholesterol [mg/dl]	102 ± 22	108 ± 35
HDL-cholesterol [mg/dl]	42 ± 14	51 ± 16

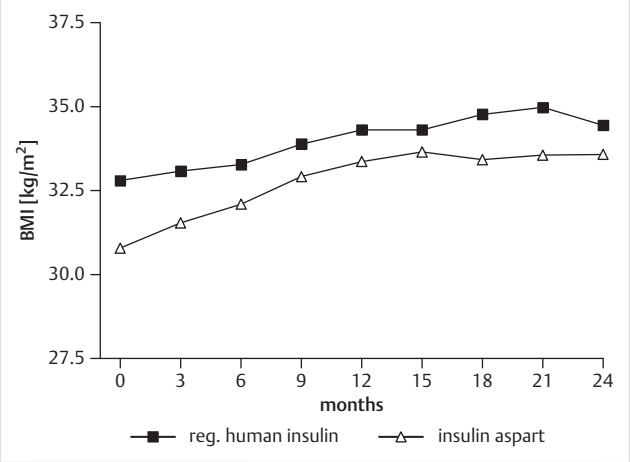

Fig. 1 Follow-up of BMI after initiation of prandial insulin treatment with regular human insulin vs. insulin aspart in 29 patients with type 2 diabetes mellitus (difference between the groups: p = n.s).

The aim of the prospective multicenter study is to compare the efficacy of insulin analogue insulin aspart concerning metabolic und cardiovascular effects in patients with type 2 diabetes mellitus in comparison with human regular insulin.

Methods

Patients with type 2 diabetes mellitus (age: 18–75 years), treated with oral antidiabetic drugs (biguanides, sulfonylureas, glinides, α-glucosidase inhibitors) for at least 6 months and a HbA1c > 7.0% were included in an open, randomised, prospective, controlled, multicenter parallel-group study over a period of 24 months. Patients were randomized in 2 groups. Group 1 (IA-group) received insulin aspart (NovoRapid® 100 U/ml, solution for injection) in a pre-filled syringe (FlexPen® 3 ml). Group 2 (RHI-group) received regular human insulin (Actrapid® 100 U/ml, solution for injection) in a pre-filled syringe (NovoLet®, 3 ml).

Insulin aspart or regular human insulin started with a dosage of 8 I.E. before each meal. Insulin aspart versus human insulin was treated to < 140 mg/dl postprandial. Insulin detemir ((Levemir® 100 U/ml, solution for injection) in a pre-filled syringe (FlexPen®, 3 ml) was treated to < 110 mg/dl in the morning (fasting). Insulin detemir started at bedtime (10.00–11.00 p.m.) after a previous dose titration of insulin aspart or regular human insulin over 6 months of treatment. The initial dosage of insulin detemir or NPH-insulin was 8 I.E. and could not be given alone. Daily blood glucose levels were documented (fasting, 2 h after breakfast, before lunch, dinner and night [10.00–11.00 p.m.]) and insulin dosage was adjusted with 2 I.E. weekly in the first month, and monthly further-on. In case of hypoglycemia insulin dosage was reduced to the lower dosage of the titration-table. Insulin dosage was adjusted each week if necessary. The Patients were visited every 3 months. At each visit BMI, waist circumference, HbA1c, fasting plasma glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, adiponectin were determined (**Table 1**).

Adiponectin concentrations were measured on diluted (1:500) fasting serum samples using a human adiponectin radioimmunoassay (RIA) kit (Linco Research, Missouri, USA). The sensitivity of the assay was 1 µg/ml and the limit of linearity 200 µg/ml. All samples were run in duplicate in the same assay. The mean intra- and inter-assay coefficient of variation was 6% and 9%, respectively.

Blood glucose was measured by accu check aviva BZMS (Roche Diagnostics GmbH, Mannheim, Germany) in all included patients. Each study center received computer based software (accu-check camit pro 360° software) to collect all data of time-defined blood glucose. Each blood glucose level was documented in a blood glucose diary sheet.

Statistics

Wilcoxon/Mann/Whitney test (WMW). Absolute differences between time-points will be analyzed per group using the paired Wilcoxon signed rank test (WSR). Occurrence of side effects will be compared by chi-square test (CHI). All p-values will be given unadjusted and therefore be interpreted explorative. All tests will be conducted at a 2-sided significance level at 5%. Univariate analyses will be performed with RM ANOVA. For analysis of the time courses of parameters by RM ANOVA, data from all patients will be included.

Results

29 patients (19 males, 10 females) with a mean age 59 ± 11 (mean ± SD) years (range 24–75) and treated with oral drugs for at least 6 months and a HbA1c > 7.0% were included. 7/11 of the RHI-group received additional insulin detemir and 13/18 of the IA-group. HbA1c reduced significantly in both groups (8.7 ± 1.6 to 7.2 ± 0.9 in the RHI-group ($p < 0.05$) vs. 8.7 ± 1.6 to 7.3 ± 0.9 ($p < 0.05$) in the IA-group) without significant difference between the groups over the period of time. No significant changes were seen between the 2 groups during the 24 months period in terms of BMI, waist circumference, fasting plasma glucose and lipids (**Fig. 1–3**). HDL-, LDL-, total-cholesterol levels as well as triglycerides did not change during treatment period in each group and did not differ between the groups. 3/11 in the RHI-group and 6/18 in the IA-group received lipid lowering drugs. Adiponectin serum levels decreased over the time without difference between the groups (7.9 ± 4.0 to 5.0 ± 2.0 in the RHI-group ($p < 0.03$) vs. 7.3 ± 3.4 to 4.8 ± 2.8 in the IA-group ($p < 0.0001$)). BMI slightly increased over the time (32.8 ± 4.7 to 34.5 ± 7.2 in the RHI-group (p = n.s.) vs. 31.5 ± 5.8 to 34.1 ± 6.4 in the IA-group ($p = 0.001$)) without difference between the 2 groups. During the first 9 months, the insulin dosage to reach the postprandial blood glucose < 140 mg/dl, were significantly lower in the IA-group, but approached the following the

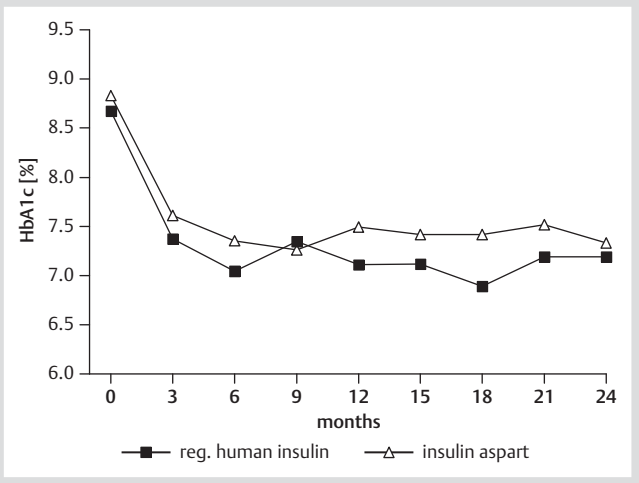

Fig. 2 Follow-up of HbA1c after initiation of prandial insulin treatment with regular human insulin vs. insulin aspart in 29 patients with type 2 diabetes mellitus (difference between the groups: p = n.s).

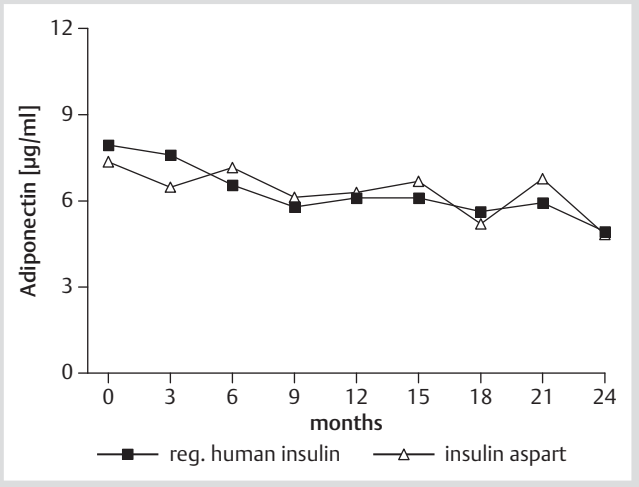

Fig. 3 Follow-up of adiponectin after initiation of prandial insulin treatment with regular human insulin vs. insulin aspart in 29 patients with type 2 diabetes mellitus (difference between the groups: p = n.s).

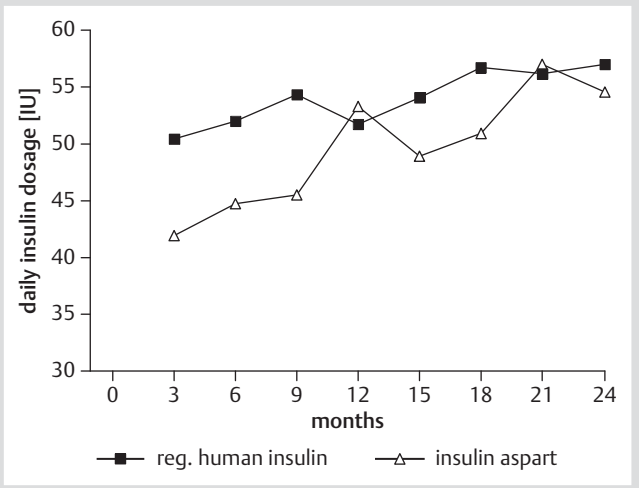

Fig. 4 Follow-up of mean insulin dosage after initiation of prandial insulin treatment with regular human insulin vs. insulin aspart in 29 patients with type 2 diabetes mellitus (difference between the groups at the end of 24 months: p = n.s).

RHI-group without significant changes after 24 months. 3/11 in the RHI-group and 5/18 in the IA-group had up to 3 episodes per year of hypoglycemia (**Fig. 4**).

Discussion

The present study has shown, that insulin aspart in comparison to normal regular insulin has no substantial benefits to metabolic parameters in patients with type 2 diabetes mellitus over a period of 24 months. BMI, waist circumference, lipids, HbA1c and adiponectin serum levels did not differ between the 2 groups.

Due to the recommendations and guidelines, insulin should be initated when HbA1c cannot be reduced < 7.0% with oral antidiabetic drugs [4, 12]. Whether basal insulin analogs are superior to NPH insulin as well as rapid-acting analogs to regular insulin is under discussion [13]. Moreover, these studies focusing to this topic should be devided in those which examine patients with type 1 or type 2 diabetes mellitus. In patients with type 1 diabetes, basis-bolus therapy using insulin detemir/insulin apart offers a better balance of control, tolerability and lower risk of hypoglycemia than with NPH/regular human insulin [8].

In terms of patients with type 2 diabetes mellitus receiving rapid-acting insulin, the additional treatment with insulin glargin vs. NPH insulin improves statistically significant HbA1c by −0.49% in comparison to the statistically not significant reduction −0.12% after a 18-months period [14]. Acute effects in lowering postprandial blood glucose in hospitalized patients with type 2 diabetes are similar if 2 different regimes are used: detemir plus aspart or NPH plus regular. In the Cochrane Database, including 8274 participants in 49 randomized controlled studies to compare rapid acting insulin analogs versus regular human insulin, the weighted mean difference of HbA1c was 0.0% in type 2 diabetes and only −0.1% in type 1 diabetes [7]. In these studies, the switch to insulin analogs from regular human short acting insulin in patients with type 2 diabetes has no substantial effects in terms of HbA1c. In the present study, we also found no difference of HbA1c reduction between insulin aspart and regular insulin.

In patients treated with long acting insulin analogs alone or added to oral antidiabetics, the beneficial effect of the slight improvement of the HbA1c reduction over a longer period of time may be due to the less weight gain [15]. This has been shown after 3 years treatment in patients with type 2 diabetes receiving insulin detemir in comparison to prandial or biphasic insulin with insulin aspart [16]. The difference of weight gain development is less pronounced between rapid acting insulin and regular insulin, as it has been shown in the present study.

Although the rates of hypoglycemia were not primary endpoints in the present study, it could be documented in other trials that weight gain correlates positively with hypoglycemic episodes when prandial insulin is used [17]. To reduce rates of hypoglycemia, several diabetes associations recommend long acting analogs added to metformin in the management of type 2 diabetes mellitus [12, 15].

Rapid acting insulin analogs in comparison to regular human insulin have the advantage of better post-meal glucose control with the consequence of lower daytime glucose fluctuations. The question is, whether these lower glucose fluctuations may improve insulin sensitivity. In the last years, it could be demonstrated that post-challenge hyperglycaemia may improve insulin

sensitivity and is an independent predictor of an increased cardiovascular mortality [18, 19].

Central obesity is associated with low adiponectin serum levels, which is an established biomarker for insulin sensitivity and maybe for cardiovascular diseases [20]. Whether adiponectin levels correlate positively or negatively with cardiovascular end-stage disease is not conclusive [11]. In 2004, it has been shown that high adiponectin levels are associated with lower risk of myocardial infarction in men, whereas other studies could documented a positive correlation with cardiovascular mortality [21, 22]. In the present study, over the period of 24 months, adiponectin serum levels decreased and did not differ significantly between the 2 groups, indicating minor influence of adipocytokines as a cardiovascular marker.

Despite the small group of patients, we can conclude that there is no evidence to date that rapid-acting analogs are superior to human regular insulin in terms of metabolism or surrogate parameters of the cardiovascular risk. Optimizing HbA1c with less rates of hypoglycemia is the primary achievement of insulin treatment [23, 24].

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Conflict of interest: None.

References

1 *Laakso M*. Hyperglycemia and cardiovascular disease in type 2 diabetes. Diabetes May 1999; 48: 937–942
2 *Eckel RH*, *Alberti KG*, *Grundy SM et al.* The metabolic syndrome. Lancet Jan 16 2010; 375: 181–183
3 *Cavalot F*, *Pagliarino A*, *Valle M et al.* Postprandial blood glucose predicts cardiovascular events and all-cause mortality in type 2 diabetes in a 14-year follow-up: lessons from the San Luigi Gonzaga Diabetes Study. Diabetes Care Oct 2011; 34: 2237–2243
4 *Nathan DM*, *Buse JB*, *Davidson MB et al.* Management of hyperglycaemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia 2006; 49: 1711–1721
5 *Ceriello A*. The possible role of postprandial hyperglycaemia in the pathogenesis of diabetic complications. Diabetologia 2003; 46: (Suppl 1): M9–M16
6 *Blaak EE*, *Antoine JM*, *Benton D et al.* Impact of postprandial glycaemia on health and prevention of disease. Obes Rev 2012
7 *Siebenhofer A*, *Plank J*, *Berghold A et al.* Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus. Cochrane Database Syst Rev 2006: CD003287
8 *Hermansen K*, *Fontaine P*, *Kukolja KK et al.* Insulin analogues (insulin detemir and insulin aspart) versus traditional human insulins (NPH insulin and regular human insulin) in basal-bolus therapy for patients with type 1 diabetes. Diabetologia 2004; 47: 622–629
9 *Menzaghi C*, *Trischitta V*, *Doria A*. Genetic influences of adiponectin on insulin resistance, type 2 diabetes, and cardiovascular disease. Diabetes 2007; 56: 1198–1209
10 *Herrmann BL*, *Saller B*, *Stratmann M et al.* Effects of a combination of rhGH and metformin on adiponectin levels in patients with metabolic syndrome. Horm Metab Res 2005; 37: 49–52
11 *Turer AT*, *Scherer PE*. Adiponectin: mechanistic insights and clinical implications. Diabetologia 2012
12 *Schernthaner G*, *Barnett AH*, *Betteridge DJ et al.* Is the ADA/EASD algorithm for the management of type 2 diabetes (January 2009) based on evidence or opinion? A critical analysis. Diabetologia 2010; 53: 1258–1269
13 *Gram J*, *Henriksen JE*, *Grodum E et al.* Pharmacological treatment of the pathogenetic defects in type 2 diabetes: the randomized multicenter South Danish Diabetes Study. Diabetes Care 2011; 34: 27–33
14 *Siegmund T*, *Weber S*, *Blankenfeld H et al.* Comparison of insulin glargine versus NPH insulin in people with Type 2 diabetes mellitus under outpatient-clinic conditions for 18 months using a basal-bolus regimen with a rapid-acting insulin analogue as mealtime insulin. Exp Clin Endocrinol Diabetes 2007; 115: 349–353
15 *Bretzel RG*, *Nuber U*, *Landgraf W et al.* Once-daily basal insulin glargine versus thrice-daily prandial insulin lispro in people with type 2 diabetes on oral hypoglycaemic agents (APOLLO): an open randomised controlled trial. Lancet 2008; 371: 1073–1084
16 *Holman RR*, *Farmer AJ*, *Davies MJ et al.* Three-year efficacy of complex insulin regimens in type 2 diabetes. N Engl J Med 2009; 361: 1736–1747
17 *Gross JL*, *Kramer CK*, *Leitao CB et al.* Effect of antihyperglycemic agents added to metformin and a sulfonylurea on glycemic control and weight gain in type 2 diabetes: a network meta-analysis. Ann Intern Med 2011; 154: 672–679
18 *Crandall JP*, *Shamoon H*, *Cohen HW et al.* Post-challenge hyperglycemia in older adults is associated with increased cardiovascular risk profile. J Clin Endocrinol Metab 2009; 94: 1595–1601
19 *Silbernagel G*, *Sourij H*, *Grammer TB et al.* Isolated post-challenge hyperglycaemia predicts increased cardiovascular mortality. Atherosclerosis 2012
20 *Zhu N*, *Pankow JS*, *Ballantyne CM et al.* High-molecular-weight adiponectin and the risk of type 2 diabetes in the ARIC study. J Clin Endocrinol Metab 2010; 95: 5097–5104
21 *Pischon T*, *Girman CJ*, *Hotamisligil GS et al.* Plasma adiponectin levels and risk of myocardial infarction in men. JAMA 2004; 291: 1730–1737
22 *Cavusoglu E*, *Ruwende C*, *Chopra V et al.* Adiponectin is an independent predictor of all-cause mortality, cardiac mortality, and myocardial infarction in patients presenting with chest pain. Eur Heart J 2006; 27: 2300–2309
23 *Dluhy RG*, *McMahon GT*. Intensive glycemic control in the ACCORD and ADVANCE trials. N Engl J Med 2008; 358: 2630–2633
24 *Seaquist ER*, *Miller ME*, *Bonds DE et al.* The impact of frequent and unrecognized hypoglycemia on mortality in the ACCORD study. Diabetes Care 2012; 35: 409–414