Insulin requirements in patients with diabetes and declining kidney function: differences between insulin analogues and human insulin?

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Abstract

Objectives: In diabetic nephropathy the decline of renal function causes modifications of the insulin and carbohydrate metabolism resulting in changed insulin requirements. The aim of the present study was to identify potential differences in the requirements of human insulin and various insulin analogues in patients with type 1 diabetes mellitus and renal dysfunction.

Methods: The insulin requirements of 346 patients with type 1 diabetes mellitus under everyday life circumstances were assessed in an observational study. Simultaneously, laboratory parameters were measured and the estimated glomerular filtration rate (eGFR) was calculated using the formula by Cockcroft–Gault. Medical history and concomitant medication were recorded. The insulin requirements of long- and short-acting insulin were tested for a relationship with the eGFR and laboratory parameters.

Results: The dosage of long-acting human insulin did not show any relation to eGFR. In contrast, a strong positive relation between dosage and renal function was found for insulin glargine and insulin detemir. After classification according to renal function, the insulin dosage at eGFR less than 60 ml/min was 29.7% lower in glargine-treated and 27.3% lower in detemir-treated patients compared with eGFR greater than 90 ml/min. Considering the whole range of eGFR, short-acting human insulin did not show a relation with renal function. Only after classification according to renal function was a dose reduction found for human insulin at eGFR less than 60 ml/min. In contrast, requirements of insulin lispro were significantly related to eGFR over the whole range of eGFR. At eGFR less than 60 ml/min the insulin dosage was 32.6% lower than at eGFR greater than 90 ml/min. The requirements of insulin aspart did not show any association with the eGFR.

Conclusions: Patients with type 1 diabetes mellitus show different insulin requirements according to the renal function depending on the applied insulin. This finding is essential for the adjustment of insulin therapy in patients with diabetic nephropathy to achieve balanced glycemic control. To determine the underlying mechanisms, further studies on the pharmacokinetics and pharmacodynamics of the different insulins in patients with diabetic nephropathy are needed.

Keywords: diabetic nephropathy, renal insufficiency, insulin requirement, human insulin, insulin analogues, insulin glargine, insulin detemir, insulin lispro, insulin aspart

Introduction

After the onset of diabetic nephropathy, further progression of renal complications and overall life expectancy are determined by the glycemic control [The Diabetes Control and Complications Trial Research Group, 1993; Gaede *et al.* 2003].

The loss of glomerular filtration rate (GFR) is associated with alterations of the carbohydrate metabolism due to pharmacokinetic and pharmacodynamic changes of insulin [Eidemark *et al.* 1995; Svensson *et al.* 2002; Alvestrand *et al.* 1989; Charlesworth *et al.* 2005]. Development of

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diabetic nephropathy is therefore commonly accompanied by a difficult metabolic control, particularly an increased risk of hypoglycemia [Iglesias and Díez, 2008]. Besides the intrinsic clinical relevance, hypoglycemic episodes constitute an independent cardiovascular risk factor [Zoungas *et al* 2010]. Thus adequate optimization of glycemic control requires fundamental knowledge of the altered pharmacokinetics and pharmacodynamics of insulin in patients with diabetic nephropathy. Whereas the pharmacological properties in renal insufficiency are at least in part well characterized for oral antidiabetic drugs, there is little information about the characteristics of insulin, particularly the insulin analogues [Iglesias and Díez, 2008; Biesenbach *et al* 2003; Hasslacher *et al.* 2007; Rave *et al.* 2001; Holmes *et al.* 2005; Lindholm and Jacobson, 2001; Bolli *et al.* 2012]. We could recently show differences between the insulin requirements of human insulin *versus* insulin analogues [Hasslacher *et al.* 2007]. The aim of the present observational study was to determine the correlation of the insulin requirements and the renal function separately for long-acting insulin (human insulin, insulin glargine, insulin detemir) and short-acting insulin (human insulin, insulin lispro, insulin aspart) under everyday life circumstances.

Patients and methods

A total of 346 patients with type 1 diabetes who attended the outpatient clinic of St. Josefskrankenhaus Heidelberg were included in the study according to the following inclusion criteria: age 20–85 years, duration of diabetes over 5 years, intensified insulin therapy, no change in the applied insulin or dosage during the previous 3 months. Patients with diabetes demanding more than 1.2 IU/kg body weight/day (IU/kg bw/day) were excluded from the study due to apparent insulin resistance as well as patients with pronounced obesity [body mass index (BMI) > 35 kg/m²], acute infection, chronic or consuming disease. Further reasons for exclusion were administration of systemic glucocorticoid therapy and hemodialysis. Patients were classified according to the applied long-acting insulin [human insulin (Huminsulin basal (Lilly Deutschland GmbH, Giessen, Germany), Insuman basal (Sanofi-Aventis Deutschland GmbH, Frankfurt, Germany), Protaphane (Novo Nordisk Pharma GmbH, Mainz, Germany)), insulin glargine, insulin detemir] and the short-acting insulin [human insulin (Huminsulin normal, Insuman Rapid, Actrapid (Novo Nordisk Pharma GmbH, Mainz, Germany)), insulin lispro, insulin aspart]. To assess the adequate

requirements of long-acting insulin, the dose of long-acting insulin was adjusted according to meal omission before participation in the present study.

At the beginning of the study biometric and demographic data (body height and weight, BMI, age, and duration of diabetes) as well as laboratory parameters [hemoglobin A_{1c} (HbA_{1c}), serum creatinine, serum lipids, hemoglobin, leukocyte count, high sensitivity C-reactive protein (hsCRP), urinalysis, and proteinuria] and the history of cardiovascular complications and concomitant therapy were recorded.

Renal function was determined as the estimated GFR (eGFR) using the Cockcroft–Gault formula. The stages of nephropathy were classified according to the international standard. For evaluation of the insulin dosage required under everyday life circumstances the patients were asked to document the amount of insulin units applied on three subsequent days after the study visit. Based on those data the mean daily requirements of long- and short-acting insulin were calculated as IU/kg bw/day.

The study was approved by the local ethics committee and was conducted according to the Declaration of Helsinki. All subjects provided written informed consent prior to participation.

Statistical evaluation was performed using MedCalc (Version 11.1.1.0, MedCalc Software, Mariakerke, Belgium). For descriptive analysis the mean and the standard deviation as well as relative and absolute frequencies were calculated. The continuous variables in Tables 1–3 were compared by using analysis of variance, whereas for comparison of frequencies the Fisher's exact test was used. The mean insulin doses of long- and short-acting insulin of the different groups classified according to the eGFR were compared by using the *t* test.

Due to the observational study design used for investigation of the impact of the eGFR on the insulin requirements, there was no randomization of the patients. We conducted univariate analyses to identify factors potentially influencing the insulin requirements. Available covariates for adjustment were age, sex, duration of diabetes, BMI, HbA_{1c}, hemoglobin, hsCRP, and concomitant therapy with β blockers. The potential confounders were taken into consideration as covariates in multiple regression models. Results were considered statistically significant when $p < 0.05$.

Table 1. Number of patients, demographic characteristics, BMI (mean $\pm$ standard deviation), and prevalence of arterial hypertension and macrovascular complications, classified according to the applied insulin.

	Human insulin	Insulin glargine	Insulin detemir	Insulin lispro	Insulin aspart	Total
Patients, <i>n</i> (men/women)	127 (61/66)	111 (67/44)	76 (41/35)	118 (66/52)	93 (48/45)	346 (182/164)
Age, years	50.5 $\pm$ 14.8	49.9 $\pm$ 14.8	53.7 $\pm$ 11.6	48.7 $\pm$ 13.7	52.0 $\pm$ 13.3	50.7 $\pm$ 14.1
Duration of diabetes, years	20.5 $\pm$ 12.0	21.8 $\pm$ 13.0	21.9 $\pm$ 12.2	21.7 $\pm$ 12.3	22.6 $\pm$ 12.2	21.5 $\pm$ 12.2
BMI, kg/m²	25.2 $\pm$ 3.3	25.3 $\pm$ 3.1	26.6 $\pm$ 5.3	25.5 $\pm$ 4.1	26.1 $\pm$ 3.8	25.5 $\pm$ 3.8
Arterial hypertension, %	60	61	67	58	60	61
Macrovascular complications, %	22	13	20	14	16	17

Table 2. Hemoglobin A1c (HbA_{1c}) and plasma glucose (mean $\pm$ standard deviation), classified according to the applied insulin.

	Human Insulin	Insulin glargine	Insulin detemir	Insulin lispro	Insulin aspart
HbA_{1c}, %	7.6 $\pm$ 1.5	7.5 $\pm$ 1.3	7.9 $\pm$ 1.1	7.4 $\pm$ 1.2	7.8 $\pm$ 1.3
Mean (3 days) premeal plasma glucose					
Breakfast	136.1 $\pm$ 23.3	137.7 $\pm$ 49.8	138.7 $\pm$ 47.3	135.7 $\pm$ 51.6	134.6 $\pm$ 36.2
Lunch	133.9 $\pm$ 39.9	133 $\pm$ 54.8	133.5 $\pm$ 51	130.2 $\pm$ 50.3	130.9 $\pm$ 57.4
Dinner	143.7 $\pm$ 45.6	151.8 $\pm$ 59.4	149.6 $\pm$ 51.9	152 $\pm$ 68.3	152 $\pm$ 64.8

Results

All 346 patients included in the study performed a kind of intensified insulin therapy: 65 of the patients were on an intensified conventional insulin therapy, 231 patients applied a functional insulin therapy, 50 patients used an insulin pump for a continuous subcutaneous insulin injection. A summary of the demographic and biometric data as well as the prevalence of relevant concomitant diseases of the total group and the subgroups is given in Table 1. There was no relevant difference between the subgroups concerning age, duration of diabetes, BMI, and the prevalence of arterial hypertension and macrovascular concomitant diseases. As shown in Table 2 there were no significant differences concerning the HbA_{1c} and the mean premeal plasma glucose, that is, sufficient and comparable glycemic control was provided by the recorded insulin doses.

The main laboratory findings are summarized in Table 3. Except for a slightly higher eGFR in patients treated with insulin glargine or lispro there were no significant differences between the subgroups concerning the laboratory parameters.

Forty-four percent of the patients with diabetes included in the study showed no sign of diabetic

nephropathy at all (i.e. eGFR > 90 ml/min and albuminuria < 20 mg/liter). In 6% of the patients normal eGFR greater than 90 ml/min was accompanied by increased albuminuria (>20 mg/liter). A reduced eGFR was found in the other half of the study population: 34% of the subjects showed a mild (60–89 ml/min), 13% a moderate (30–59 ml/min) and 3% a severe reduction of eGFR (15–29 ml/min).

Requirements of long-acting insulin

The relations between the renal function and the required dosage of long-acting insulin (human insulin, insulin glargine, and insulin detemir) are shown in Figure 1(a–c). The results of the regression analyses can be found in Table 4.

The required dosage of long-acting human insulin was widely scattered (0.05–0.66 IU/kg bw/day) over the whole range of eGFR. There was no correlation to the renal function [Figure 1(a); $p = 0.141$]. In contrast, the dosages of insulin glargine ($p = 0.0003$) as well as insulin detemir ($p = 0.0015$) were significantly related to the eGFR: a lower glomerular filtration rate was associated with lower dosages of insulin [Figure 1(b, c)].

Figure 2 illustrates the mean daily requirements of long-acting insulin in patients with eGFR

Table 3. Laboratory findings (mean $\pm$ standard deviation), classified according to the applied insulin.

	Human insulin (<i>n</i> = 127)	Insulin glargine (<i>n</i> = 111)	Insulin detemir (<i>n</i> = 76)	Insulin lispro (<i>n</i> = 118)	Insulin aspart (<i>n</i> = 93)	Total (<i>n</i> = 346)
eGFR, ml/min	85.8 $\pm$ 33.8	95.3 $\pm$ 30.3	91.2 $\pm$ 32.4	97.3 $\pm$ 30.2	92.1 $\pm$ 30.0	91.3 $\pm$ 31.8
Hemoglobin, g/dl	13.7 $\pm$ 1.6	14.2 $\pm$ 1.3	13.7 $\pm$ 1.5	14.1 $\pm$ 1.4	13.9 $\pm$ 1.4	13.9 $\pm$ 1.5
Leukocyte count, number/nl	6.5 $\pm$ 2.1	6.5 $\pm$ 1.8	6.2 $\pm$ 1.8	6.4 $\pm$ 1.9	6.3 $\pm$ 1.8	6.4 $\pm$ 1.9
Total cholesterol, mg/dl	195 $\pm$ 39	194 $\pm$ 37	203 $\pm$ 48	192 $\pm$ 40	200 $\pm$ 42	195 $\pm$ 40
HDL cholesterol, mg/dl	62 $\pm$ 21	67 $\pm$ 19	60 $\pm$ 16	65 $\pm$ 20	63 $\pm$ 16	63 $\pm$ 19
LDL cholesterol, mg/dl	112 $\pm$ 35	119 $\pm$ 100	120 $\pm$ 40	106 $\pm$ 32	129 $\pm$ 109	115 $\pm$ 64
hsCRP, mg/liter	2.4 $\pm$ 2.9	2.5 $\pm$ 3.2	2.8 $\pm$ 3.0	2.5 $\pm$ 3.4	2.7 $\pm$ 2.8	2.5 $\pm$ 3.0
eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein.						

Table 4. Univariate and multiple regression analyses considering influencing factors of the insulin requirements (i.e. HbA_{1c}, hemoglobin, hsCRP, and treatment with β blockers) for the dosage (IU/kg bw/day) of various insulins in relation to 10 ml/min of eGFR (ml/min).

	Univariate regression analysis			Multiple regression analysis		
	Regression coefficient	95% confidence interval	<i>p</i>	Regression coefficient	95% confidence interval	<i>P</i>
Basal insulin requirements						
Human insulin	0.005	−0.0017 to 0.0118	0.141	0.0029	−0.0047 to 0.0104	0.46
Insulin glargine	0.0102	0.0048–0.0155	0.0003	0.0112	0.0052–0.0172	0.0004
Insulin detemir	0.0128	0.0051–0.0205	0.0015	0.0107	0.0018–0.0197	0.022
Prandial insulin requirements						
Human insulin	0.0074	−0.0021 to 0.0169	0.1247	0.0108	0.0003–0.0213	0.0462
Insulin lispro	0.0147	0.0048–0.0247	0.0041	0.0157	0.0054–0.0259	0.0034
Insulin aspart	0.001	−0.0089 to 0.011	0.8386	−0.0033	−0.014 to 0.0075	0.5558
Please note the reported estimates relate to insulin requirements per kilogram of body weight. eGFR, estimated glomerular filtration rate; HbA _{1c} , hemoglobin A _{1c} ; hsCRP, high-sensitivity C-reactive protein.						

greater than 90 ml/min, 60–89 ml/min and less than 60 ml/min. Whereas the mean dosage of long-acting human insulin was constant throughout all stages of renal filtration rate, patients with at least moderate reduction of eGFR (<60 ml/min) needed

about 29.7% less long-acting insulin than those with normal filtration rate when they were treated with insulin glargine ($p = 0.006$) and about 27.3% less when they were treated with insulin detemir ($p = 0.007$).

Figure 1. Daily dosage of (a) long-acting human insulin, (b) insulin glargine and (c) insulin detemir per kg body weight (IU/kg bw/day) in relation to estimated glomerular filtration rate (eGFR, ml/min).

Figure 2. Mean daily dosage of insulin glargine, insulin detemir, and long-acting human insulin [IU/kg body weight (bw)/day] in relation to estimated glomerular filtration rate (eGFR, ml/min).

Besides the eGFR, significant influence on the insulin requirements could also be proven for HbA1c, hemoglobin, hsCRP, and a therapy with β blockers in univariate regression analyses (not

shown). A multiple regression analysis, accounting for those influencing factors, confirmed the correlation between the insulin requirements and the renal function (Table 4).

Requirements of short-acting insulin

Short-acting human insulin did not show a relation to renal function if the whole range of eGFR was considered [Figure 3(a)]. The multiple regression analysis including the mentioned potential influencing factors of insulin resistance (HbA1c, hemoglobin, hsCRP, and therapy with β blockers) revealed a significant dose reduction for short-acting human insulin according to the loss of renal function (Table 4). Compared with an eGFR greater than 90 ml/min, an at least moderate reduction of the filtration rate (<60 ml/min) was associated with a mean dose reduction of short-acting human insulin of about 25% ($p = 0.01$).

In contrast, the requirements of insulin lispro were significantly associated with the GFR [Figure 3(b)]. This correlation was again proven by the

Figure 3. Daily dosage of (a) short-acting human insulin (b) insulin lispro and (c) insulin aspart per kg body weight (IU/kg bw/day) in relation to estimated glomerular filtration rate (eGFR, ml/min).

Figure 4. Mean daily dosage of insulin lispro, insulin aspart and short-acting human insulin [IU/kg body weight (bw)/day] in relation to estimated glomerular filtration rate (eGFR, ml/min).

multiple regression analysis (Table 4). Patients with an eGFR less than 60 ml/min needed about 32.6% less insulin lispro than patients with normal renal function ($p = 0.002$; Figure 4).

For insulin aspart there was no significant association between the eGFR and the requirements of short-acting insulin [Figures 3(c) and 4, Table 4].

Discussion

Patients with type 1 diabetes treated with an intensified insulin therapy show different insulin requirements after onset of diabetic nephropathy according to the applied insulin under everyday life circumstances. Our observational study revealed a significant dose reduction in relation to the renal function for the long-acting insulin analogues, glargine and detemir, whereas there were constant requirements of long-acting human insulin.

Regarding the short-acting insulin our findings showed significantly declining requirements for insulin lispro in the univariate as well as in the multiple regression analysis, whereas for short-acting human insulin there was only a significant association with the renal function if further influencing factors of insulin resistance were included

in the multiple regression analysis. In contrast, the required dosage of insulin aspart was not associated with the eGFR.

Changes in insulin requirements linked to a declining renal function can be attributed to altered pharmacokinetics and dynamics of insulin. Whereas about 50% of endogenously secreted insulin is cleared from the portal vein during the first passage through the liver, there is no comparable hepatic first-pass effect after subcutaneous application [Eidemak *et al.* 1995; Nielsen, 1992]. In the case of subcutaneous application of insulin the renal elimination gains major importance. Insulin is metabolized in the proximal tubular cells after glomerular filtration and is furthermore eliminated via the peritubular endothelium and in renal epithelial cells [Svensson *et al.* 2002; Alvestrand *et al.* 1989; Nielsen, 1992]. Thus, insulin clearance decreases as renal failure progresses, resulting in a prolonged pharmacokinetic profile and a demand of dose reduction to prevent hypoglycemia. The decrease in renal function is also associated with an increased insulin resistance due to reduced hepatic glucose uptake and modified intracellular glucose metabolism [Charlesworth *et al.* 2005; Duckworth *et al.* 1998; Ferrannini *et al.* 1983; Rabkin *et al.* 1984]. This process is usually accompanied by a higher insulin demand. The altered pharmacokinetics and pharmacodynamics of insulin in diabetic nephropathy may result in an unstable metabolic situation with an increased frequency and severity of hypoglycemic episodes.

Despite the importance of insulin for the treatment of patients with diabetes and renal insufficiency there is only little information on the characteristics of the approved insulins in relation to a declining glomerular filtration [Iglesias and Díez, 2008; Biesenbach *et al.* 2003; Hasslacher *et al.* 2007]. Rave and colleagues found a reduction in the clearance of regular human insulin in patients with type 1 diabetes and a mean eGFR of 54 ml/min of 30–40% [Rave *et al.* 2001]. Similarly, Biesenbach and colleagues described a 38% reduction of insulin requirements in patients with type 1 diabetes as renal function decreased from 80 to 10 ml/min [Biesenbach *et al.* 2003]. However, previous studies did not differentiate between long- and short-acting human insulin nor was there a separate analysis of the various insulin analogues.

The most distinct dose reduction was found for insulin lispro. Referring to a person with normal

renal function (eGFR > 90 ml/min) and 70 kg of body weight the mean total dosage of insulin lispro was about 32 IU/day. Assuming that the filtration rate was then reduced to less than 60 ml/min, the mean dosage of insulin lispro would have to be reduced to about 22 IU/day. For short-acting human insulin the dose reduction would be 7 IU/day (30 IU/day *versus* 23 IU/day). Provided there was a comparable quality of metabolic control this finding may indicate a stronger metabolic activity for insulin lispro than for short-acting human insulin in the presence of diabetic nephropathy. The outcome of our study thus confirms under everyday life circumstances the results of an experimental glucose clamp study performed by Rave and colleagues, which showed increased metabolic activity as well as changes in the pharmacokinetics for insulin lispro in 12 patients with type 1 and reduced renal function [Rave *et al.* 2001]. In contrast, patients with diabetes treated with insulin aspart did not show any significant change in the insulin dosage in relation to the renal filtration rate in our study. Holmes and colleagues also did not find an increase in the insulin concentration in relation to the GFR in patients with type 1 diabetes [Holmes *et al.* 2005].

There are no studies on the pharmacodynamics of long-acting human insulin and insulin glargine respectively in relation to a declining renal function. For insulin detemir, Lindholm and Jacobsen could not show significant differences in the pharmacokinetics related to the stages of renal failure [Lindholm and Jacobson, 2001]. Our study for the first time quantified the required dose reduction of long-acting insulin analogues. Given a person of 70 kg body weight and eGFR greater than 90 ml/min, the mean daily dosage was 19 IU of insulin glargine and 23 IU of insulin detemir. Provided that the eGFR was less than 60 ml/min, the doses would have to be reduced to 13 IU of glargine and 17 IU of detemir. Whether those differences in insulin requirements result from changes in degradation of the active metabolites of insulin glargine [Bolli *et al.* 2012] or from the binding of insulin detemir to albumin is yet not completely known and needs to be the subject of further studies.

A limitation of the present study might be the lack of measurement of the C peptide as an indicator for the residual endogenous insulin secretion. However, patients with a short duration of diabetes (<5 years) were excluded from the study to minimize the possible influence of endogenous

insulin. The mean duration of diabetes was 20 years. Any influence on the insulin requirements due to residual insulin secretion therefore seems implausible. Besides, in a study of patients with type 2 diabetes and renal failure, Biesenbach and colleagues did not find any impact of the C peptide on the insulin requirements [Biesenbach *et al.* 2003]. Another limitation of the study was that patients were not randomized to the applied insulin, but continued their previous therapy. As shown in Tables 1–3, there were nevertheless no relevant differences between the various subgroups concerning demographic, clinical, and laboratory findings.

An important advantage of this study was the large number of patients in all subgroups ($n = 76$ –127 patients), in contrast to previous experimental studies. Another advantage is that instead of artificial experimental settings we conducted our study under ‘real-life’ conditions. The conclusions drawn from this study therefore can be directly taken into account for everyday patient-centered care.

The results may help to improve insulin therapy by individually estimating the necessity of a dose reduction. The reasons for the different characteristics of the insulins are as yet unexplained and should be investigated. In addition to this investigation, further studies under predefined conditions need to be conducted to increase therapeutic safety in patients with insulin-dependent diabetes and renal insufficiency.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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