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Evaluation of treatment adherence in type 1 diabetes: a novel approach

T. M. Kitzler[*†], **M. Bachar**[‡], **F. Skrabal**[*] **and P. Kotanko**[*†]

[*]Krankenhaus der Barmherzigen Brüder, Graz, Austria, [†]Renal Research Institute, New York, USA, [‡]Institute for Mathematics and Scientific Computing, Graz, Austria

Abstract

Background Intensified insulin therapy requires outstanding compliance but no measure of therapy adherence has been agreed upon. The aim of the current study was to test the hypothesis that treatment adherence, as described by a novel multiple regression model, relates to glycosylated haemoglobin and hypoglycaemia frequency in type 1 diabetes. Furthermore, we sought to analyse the complex diurnal patterns of therapy adherence.

Materials and methods Thirty type 1 diabetes patients (20 females and 10 males), treated with intensified insulin therapy, were studied in a retrospective manner. Patients were trained to follow treatment algorithms for adjusting regular insulin dosage which took into account the actual blood glucose, food intake and the time of the day. By means of multiple linear regression analysis, with regular insulin dosage as the dependent variable, blood glucose and food intake as the independent variables, the insulin treatment algorithms actually used by the individual patient were retrieved. The correlation between prescribed and implemented insulin therapy served as a measure of adherence. Metabolic control was assessed by glycosylated haemoglobin and hypoglycaemia frequency.

Results Median glycosylated haemoglobin was 7·7% (range: 6·3–10·8); median monthly hypoglycaemia frequency was 3·8 (range: 0–9·8). Patients with good metabolic control (glycosylated haemoglobin < 7·7 and/or hypoglycaemia frequency < 3·8 per month) adhered to prescribed insulin dosing algorithms more frequently than those with poor metabolic control.

Conclusions In patients with type 1 diabetes on intensified therapy a positive relationship between adherence to the therapy prescribed and metabolic control exists.

Keywords Diabetes mellitus, metabolic control, therapy adherence.
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Introduction

Type 1 diabetes is accompanied by multiple sequelae, including long-term macro- and microvascular complications [1,2]. A key predictor of the development, progression or reversal of these complications is the glycosylated haemoglobin (HbA1c) level [3,4]. Intensified insulin therapy improves HbA1c levels but the risk of hypoglycaemia may increase [5–9].

Intensified insulin therapy requires outstanding compliance, frequent self-control of blood glucose levels and multiple daily injections of long-acting and regular insulin. Calculation of the regular insulin dose is accomplished by simple algorithms taking into consideration the time of day, carbohydrate intake and actual blood glucose levels.

In type 1 diabetes treatment, non-adherence, due to problems of integrating intensified therapy regimes into daily life and meeting treatment targets, is frequently observed [10,11]. Many factors affect adherence, such as social support, psycho-social stress, family functioning, marital quality, spouse's age, number of visits to a multidisciplinary diabetes clinic, the quality of interaction with healthcare providers, intensive home-based psychotherapy, the use of a blood

Department of Internal Medicine, Krankenhaus der Barmherzigen Brüder, Marschallgasse 12, A-8020 Graz, Austria (T. M. Kitzler, F. Skrabal, P. Kotanko); Renal Research Institute, 207 East 94th Street, Suite 303, New York, NY 10128, USA (T. M. Kitzler, P. Kotanko); University of Graz, Institute for Mathematics and Scientific Computing, Heinrichstrasse 36, A-8010 Graz, Austria (M. Bachar).

Correspondence to: Peter Kotanko, MD, Krankenhaus der Barmherzigen Brüder, Department of Internal Medicine, Marschallgasse 12, A-8020 Graz, Austria. Tel.: +43 31670670; fax: +43 3167067 598; e-mail: kotanko1@eunet.at

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glucose monitoring manual to enhance monitoring adherence, and the duration of diabetes [10–23]. Non-adherence may result in poor metabolic control and may increase the risk of ketoacidosis in adolescents and young adults [17,24,25]. Thus, there is a pressing need to explore this issue further [16].

A factor preventing patients from therapy adherence is fear of treatment-related hypoglycaemia. Hypoglycaemia is an adverse event of intensified insulin therapy and lower HbA1c levels are a risk factor [8,26–28].

Previous studies assessing therapy adherence scarcely employed metabolic indicators such as HbA1c as an outcome and it is still not clear if strict therapy adherence translates into improved metabolic control [17,24,25,29]. Therapy adherence was assessed either by questionnaire (e.g. the Morisky score) or by comparing prescribed insulin doses with the cumulative volume of insulin supplied by the pharmacy. So far, no 'gold standard' for assessment of therapy adherence in patients with diabetes has been agreed upon [30]. We approached the issue of therapy adherence by means of a novel multiple regression model.

Materials and methods

Study population

Thirty patients (20 females and 10 males) with type 1 diabetes were enrolled in this single-centre study at the Krankenhaus der Barmherzigen Brüder, Graz, Austria. Patients were trained on the principles and practice of intensified insulin therapy and carbohydrate counting. Patients documented relevant data (blood glucose, bread exchange units (BEU), doses of basal and regular insulin, date and time of day, and any special events) electronically using a Camit™ device. At the hospital's diabetes outpatient clinic a patient is cared for exclusively by his or her designated physician with a total of three diabetologists in charge.

All three agreed on the same principles of applying regular insulin according to predefined rules that were not changed during the course of this study.

HbA1c and monthly hypoglycaemia rates served as indicators of metabolic control. Hypoglycaemia was defined as blood glucose values below 50 mg dL^{-1} [31]. Two kinds of stratification of the study population were performed:

1 The study cohort was divided into two groups of equal size according to the median of HbA1c (groups $HbA1c_{Low}$ and $HbA1c_{High}$) or hypoglycaemia frequency (groups $Hypo_{Few}$ vs. $Hypo_{Many}$), respectively.
2 In order to obtain a more integrated picture of metabolic control, in a second analysis, patients were stratified into groups with good ($Control_{Good}$; both HbA1c and hypoglycaemia frequency below the respective medians), poor ($Control_{Poor}$; both HbA1c and hypoglycaemia frequency above the respective medians), and intermediate metabolic control ($Control_{Med}$; either HbA1c or hypoglycaemia frequency above the respective medians).

Insulin therapy

Patients were trained to adjust regular insulin prescriptions to their needs. Actual blood glucose (BG_{act}), target glucose values (BG_{target}), food intake, time of the day and physical activities were considered.

A regular insulin therapy prescription consists of two components:

1 The prandial insulin covers ingested carbohydrates (expressed as bread exchange units; 1 BEU corresponds to 12 g of carbohydrate); the prandial insulin dose is expressed as IU of regular insulin per BEU (IU/BEU); the ratio (p_1: if $BG_{act} \geq BG_{target}$; p_2: if $BG_{act} < BG_{target}$) may change during the course of the day.
2 The correction insulin is given to compensate for BG_{act} above a predefined BG_{target}; it is expressed as IU of regular insulin per mg dL^{-1} of blood glucose above target value (IU per mg dL^{-1}); the ratio (c) may vary during the day. No correction insulin is given with $BG_{act} < BG_{target}$.

Generally, the patients did not adjust basal insulin requirements. All patients used the same basal insulin, none used Detemir (Levemir® from Novo Nordisk, Bagsværd, Denmark) and only three used insulin Aspart (NovoRapid® from Novo Nordisk, Bagsværd, Denmark).

Data on clinical characteristics, laboratory measurements, prescribed insulin therapy and target blood glucose values were collected by chart review.

Renal function measures

Creatinine clearance (CrCl) was calculated using the Gault-Cockcroft formula:

$$\text{CrCl (males)} = [140\text{-age (years)}] \times [\text{body weight (kg)}]/72 \times [\text{serum creatinine (mg dL}^{-1})]$$

$$\text{CrCl (females)} = 0{\cdot}85 \times [140\text{-age (years)}] \times [\text{body weight (kg)}]/72 \times [\text{serum creatinine (mg dL}^{-1})]$$

Urinary protein/creatinine ratio was determined in the second morning urinary sample by dividing the urinary protein concentration (mg dL^{-1}) by the urinary creatinine concentration (mg dL^{-1}); a value below 0·15 is considered normal.

Statistical analyses

Continuous data are presented as mean ± standard deviation (SD) and range; differences between groups are reported as means and 95% confidence intervals (95% CI). The non-parametric Wilcoxon test was used for group comparison. For all analyses a two-sided *P*-value < 0·05 was considered significant. Multiple group comparison was done by using one-way ANOVA and a post-hoc test (Bonferroni correction).

Multiple regression models

Two regression models with regular insulin dosage (D_{rI}) as the dependent variable and ingested BEU and the difference between BG_{act} and BG_{target} as independent variables, were developed. These models reflect the prescription practice for regular insulin as described above.

(1) If $BG_{act} \geq BG_{target}$: $D_{rI} = \pi_1 \star BEU + \chi \star (BG_{act} - BG_{target})$

(2) If $BG_{act} < BG_{target}$: $D_{rI} = \pi_2 \star BEU$

The coefficients π_1 and π_2 represent estimates of the prandial insulin and χ of the correction insulin. Since these coefficients may vary in the course of the day we considered three diurnal periods: morning (5 AM to 11 AM), noon (11 AM to 4 PM), and evening (4 PM to 11 PM).

Correlation analysis

The estimated coefficients (π_1, π_2 and χ) were correlated with the respective prescribed coefficients (p_1; p_2; c) by non-parametric Spearman rank-order correlation. A higher correlation coefficient was interpreted as a higher degree of adherence to the prescribed insulin therapy. The statistical analyses were done with the SPSS version 11·5 (SPSS Inc.) and multiple regression models were programmed in MATLAB (version 6·5; the programs are available upon request from mostafa.bachar@uni-graz.at).

Results

Table 1 gives the baseline characteristics of the study population. All patients were C-peptide negative. Details about insulin therapy and blood glucose of the study population are shown in Table 2.

Table 1 Baseline characteristics of the study population ($n = 30$)

Age (years)	42 ± 12·9 (16·1–71·9)
Sex (females/males)	20/10
Type 1 diabetes onset (age)	24·5 ± 14·3 (3·4–51·9)
Duration of type 1 diabetes (years)	17·5 ± 11·5 (2–48)
Diabetic retinopathy	40%
Diabetic polyneuropathy	36%
Medical therapy	
Beta blocker	16%
ACE inhibitor	40%
Angiotensin receptor antagonist	10%
Calcium antagonist	16%
Other medication	56%
HbA1c (%)	7·9 ± 1·2 (6·3–10·8)
Mean SD of HbA1c (%)	0·5 (0·3–0·7)⋆
Serum creatinine (mg dL^{-1})	0·99 ± 0·33 (0·69–2·19)
Creatinine clearance (mL min^{-1})	92·6 ± 31·5 (31·1–165·9)
Urinary protein/creatinine ratio	0·4 ± 0·7 (0·1–3·3)
Systolic blood pressure (mmHg)	126 ± 14 (90–155)
Diastolic blood pressure (mmHg)	76 ± 6 (60–87)
Observation period per patient (months)	20·4 ± 10·5 (4·8–40·2)
Number of observation periods per patient	7·03 ± 3·4 (2–15)
Duration of single observation period (months)	3·02 ± 1·1 (1·2–5·5)

Mean ± SD (range) are shown.
⋆interquartile range.

Table 2 Insulin therapy and blood glucose (BG) of the study population

	Mean ± SD (range)
Long-acting insulin (IU per day)	22·9 ± 14·6 (2·5–78·4)
Short-acting insulin (IU per day)	16·6 ± 10·7 (4·5–61·3)
Total insulin (IU per day)	39·5 ± 23·9 (8·8–139·7)
BG morning (5 AM to 11 AM)	164 ± 32 (114–254)
BG noon (11 AM to 4 PM)	144 ± 23 (98–189)
BG evening (4 PM to 11 PM)	160 ± 34 (105–266)
BG night (11 PM to 5 AM)	148 ± 44 (68–264)
Mean daily BG (mg dL^{-1})	157 ± 30 (106–250)
BG measurements per patient	2754 ± 1396 (761–5797)

Group comparison

Stratification by HbA1c

Median HbA1c was 7·7%; 15 patients constituted the groups $HbA1c_{High}$ and $HbA1c_{Low}$, respectively. Duration of diabetes was longer in $HbA1c_{High}$ (22·2 vs. 12·7 years; difference 9·5 years, 95% CI: 1·5–17·4 years, $P = 0·018$). In 13 $HbA1c_{High}$ and in 7 of $HbA1c_{Low}$ the duration of patients' diabetes exceeded 10 years.

Mean blood glucose was higher in $HbA1c_{High}$ (177 vs. 137 mg dL^{-1}; difference 40 mg dL^{-1}, 95% CI: 24–56 mg dL^{-1}, $P < 0·001$). Target blood glucose was lower in $HbA1c_{Low}$ (109 vs. 122 mg dL^{-1}; difference 13 mg dL^{-1}, 95% CI: 1–26 mg dL^{-1}, $P = 0·046$).

Creatinine clearance did not differ significantly between the groups ($HbA1c_{High}$: 82·6; $HbA1c_{Low}$: 102·5 mL min^{-1}; difference 19·9 mL min^{-1}, 95% CI: − 2·8–42·6 mL min^{-1}, $P = 0·084$); the urinary protein/creatinine ratio was higher in $HbA1c_{High}$ (0·72 vs. 0·1; difference 0·62, 95% CI: 0·11–1·12, $P = 0·004$).

Stratification by hypoglycaemia frequency

Median hypoglycaemia frequency was 3·8 events per month; 15 patients each constituted the groups $Hypo_{Many}$ and $Hypo_{Few}$, respectively. Duration of diabetes was 11·1 years longer in $Hypo_{Many}$ (23 vs. 11·9 years; 95% CI: 3·5–18·7 years, $P = 0·021$), and onset of diabetes occurred 10·4 years earlier (19·3 vs. 29·7 years; 95% CI: 0·3–20·5 years, $P = 0·021$).

Both creatinine clearance (98·8 vs. 86·4 mL min^{-1}; difference 12·4 mL min^{-1}, 95% CI: −11·1–35·9 mL min^{-1}, $P = 0·33$) and urinary protein/creatinine ratio (0·38 vs. 0·44;

difference 0·06, 95% CI: –0·62–0·5, $P = 0·401$) did not differ significantly between $Hypo_{Few}$ and $Hypo_{Many}$.

In eight $Hypo_{Few}$ patients diabetes duration exceeded 10 years and in 12 of $Hypo_{Many}$. Patients' allocation to groups $HbA1c_{Low}$ or $HbA1c_{High}$ and to groups $Hypo_{Few}$ or $Hypo_{Many}$, respectively, was unrelated ($\chi^2 = 1·2$; $P = 0·466$; 1 d.f.).

Stratification by the composite of HbA1c and hypoglycaemia frequency

In six patients both HbA1c and hypoglycaemia frequency were either below ($Control_{Good}$) or above ($Control_{Poor}$) the respective median values. In 18 patients either HbA1c or hypoglycaemia frequency were above the respective medians ($Control_{Med}$).

Duration of diabetes was longer in $Control_{Poor}$ when compared to $Control_{Med}$ (34·2 vs. 14·9 years; difference 19·3 years, 95% CI: 10·2–28·4 years, $P < 0·001$) and $Control_{Good}$ (34·2 vs. 8·5 years; difference 25·7 years, 95% CI: 14·5–36·8 years, $P < 0·001$). Diabetes duration exceeded 10 years in 1 patient of $Control_{Good}$, in 13 patients of $Control_{Med}$ and in all 6 patients of $Control_{Poor}$.

Mean blood glucose was significantly higher in $Control_{Poor}$ as compared to $Control_{Good}$ (177 vs. 131 mg dL^{-1}; difference 46 mg dL^{-1}, 95% CI: 7–84 mg dL^{-1}, $P = 0·017$) and did not differ in both groups from $Control_{Med}$.

Serum creatinine was higher in $Control_{Poor}$ when compared with $Control_{Med}$ (1·37 vs. 0·89 mg dL^{-1}; difference 0·49 mg dL^{-1}, 95% CI: 0·15–0·82 mg dL^{-1}, $P = 0·003$) and $Control_{Good}$ (1·37 vs. 0·92 mg dL^{-1}; difference 0·45 mg dL^{-1}, 95% CI: 0·04–0·86 mg dL^{-1}, $P = 0·026$). Creatinine clearance was significantly higher in $Control_{Med}$ when compared to group $Control_{Poor}$ (100 vs. 61·3 mL min^{-1}; difference 38·7 mL min^{-1}, 95% CI: 4·8–72·6 mL min^{-1}, $P = 0·021$), but it was not significantly higher in $Control_{Good}$ as compared to $Control_{Poor}$ (101·6 vs. 61·3 mL min^{-1}; difference 40·4 mL min^{-1}, 95% CI: –1·1–81·9 mL min^{-1}, $P = 0·059$). Urinary protein/creatinine ratio did not differ significantly between groups $Control_{Good}$ and $Control_{Poor}$ (0·11 vs. 0·95; difference 0·84, 95% CI: –1·87–0·18, $P = 0·137$) as well as between groups $Control_{Med}$ and $Control_{Poor}$ (0·33 vs. 0·95; difference 0·62, 95% CI: –1·46–0·22, $P = 0·209$).

Correlation analysis

$HbA1c_{Low}$ versus $HbA1c_{High}$ (Fig. 1a)

Adherence to basal insulin prescriptions was highly significant in both groups (all $P < 0·001$; data not shown). With actual blood glucose values below the target value, prandial insulins were correlated only in the $HbA1c_{Low}$ group in the morning and the evening, respectively. With actual blood glucose values above the target value prescribed and applied prandial insulins were significantly correlated in both groups, in contrast to $HbA1c_{Low}$ no correlation was observed in $HbA1c_{High}$ with respect to correction insulin. In summary, in seven out of nine scenarios a significant correlation was observed in $HbA1c_{Low}$ and in only three out of nine in $HbA1c_{High}$.

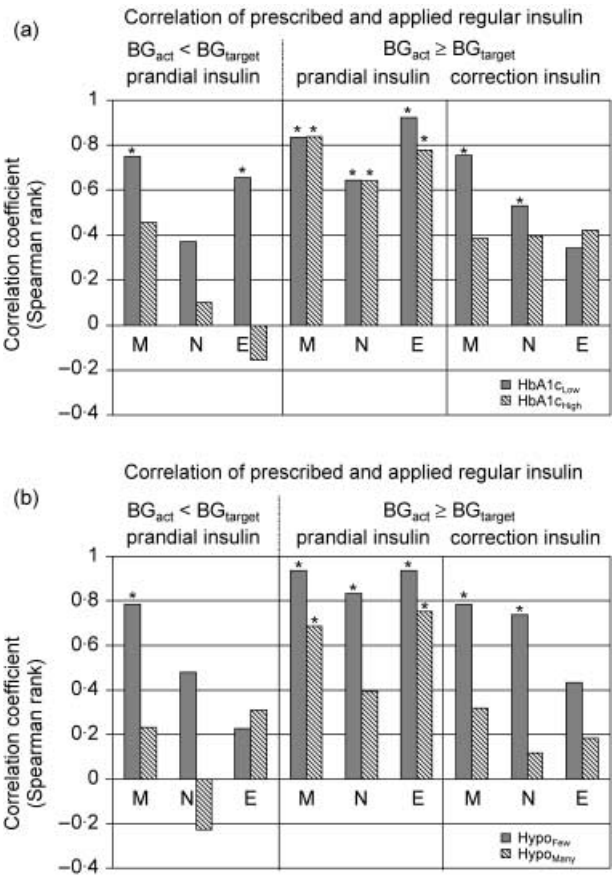

Figure 1 Spearman rank correlation coefficients (r_s) of prescribed and applied regular insulin therapies in the morning (M), at noon (N), and in the evening (E) for both prandial and correction insulin for the groups $HbA1c_{Low}$ ($n = 15$) and $HbA1c_{High}$ ($n = 15$) (Figure 1a) and the groups $Hypo_{Few}$ ($n = 15$) and $Hypo_{Many}$ ($n = 15$) (Figure 1b) are shown. *Denotes $r_s \neq 0$ ($P < 0·05$).

$Hypo_{Few}$ and $Hypo_{Many}$ groups (Fig. 1b)

Both groups adhered equally well to basal insulin prescriptions in the morning and in the evening (all $P < 0·001$; data not shown). With actual blood glucose values below the target blood glucose values only morning prandial insulins were correlated in $Hypo_{Few}$. With actual blood glucose values above the target blood glucose prescribed, applied insulins were higher correlated on all occasions in the $Hypo_{Few}$ group. At no time point was actually applied correction insulin correlated with prescribed correction insulin in $Hypo_{Many}$. In summary, in six out of nine clinical scenarios a significant correlation was observed in $Hypo_{Few}$ and in only two out of nine in $Hypo_{Many}$.

$Control_{Good}$, $Control_{Med}$, and $Control_{Poor}$ (Fig. 2)

Interestingly, $Control_{Good}$ showed no significant adherence to the basal insulin prescriptions, whereas groups $Control_{Med}$, and $Control_{Poor}$ did (all $P < 0·001$ level; data not shown). On no occasion were prescribed and applied regular insulin therapy

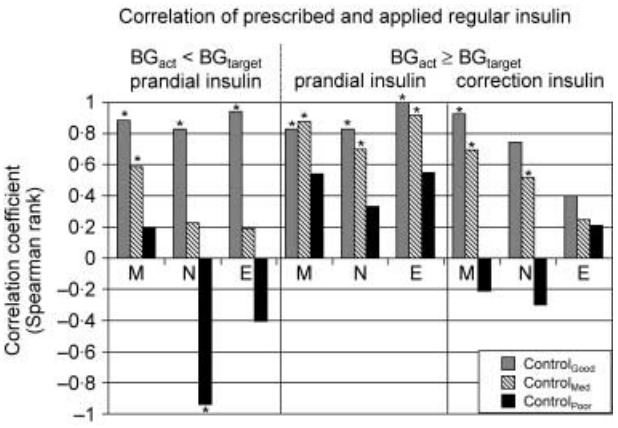

Figure 2 Spearman rank correlation coefficients (r_s) of prescribed and applied regular insulin therapies in the morning (M), at noon (N), and in the evening (E) for both prandial and correction insulin for the groups $Control_{Good}$ ($n = 6$), $Control_{Med}$ ($n = 12$), and $Control_{Poor}$ ($n = 6$) are shown (for details see text). *Denotes $r_s \neq 0$ ($P < 0{\cdot}05$).

significantly positively correlated in $Control_{Poor}$; notably, a significant negative correlation was observed in $Control_{Poor}$ at noon with actual blood glucose values below the target blood glucose values. In summary, in seven out of nine scenarios a significant positive correlation between administered and prescribed insulin was observed in $Control_{Good}$, in two out of nine in $Control_{Med}$ and in none of the 9 in $Control_{Poor}$.

Discussion

Therapy adherence to prescribed algorithms of intensified insulin therapy relates to the quality of metabolic control.

We employed a novel method to define adherence. By this method adherence can be described in a quantitatively meaningful manner. These quantitative measures can be related to indicators of metabolic control. Furthermore, this approach allows analysing patients' diurnal patterns of therapy adherence.

Our results clearly show that the strength of therapy adherence parallels metabolic control such as HbA1c, hypoglycaemia frequency or a combination of both. Despite different methodologies our results are corroborated by earlier reports on the relation between adherence and metabolic control in type 1 diabetes [17,24,25]. These studies on therapy adherence were assessed either by questionnaires or by comparison of the medically recommended insulin doses to cumulative volumes of insulin supplied.

Admittedly, there are limitations to our study. The study was performed in a non-randomized retrospective manner. Therefore, we were not able to control for confounding variables such as duration of diabetes or gender. The distribution between males and females was also not balanced, with more female patients than males. Also, in female patients the influence of hormone cycling has to be considered. Women also require higher doses of insulin during the gestagen phase due to a decreased sensitivity to insulin in the peripheral fat tissue.

The longer duration of diabetes in the groups with poorer metabolic control may have had an adverse effect on therapy adherence. Since the number of patients participating in the evaluation is rather small we were unable to perform an analysis stratified according to gender or diabetes duration.

Duration of diabetes may affect metabolic control and therapy adherence adversely [12,24,32–34]. Shorter duration relates to greater family and social support, which may translate into better therapy adherence with improved metabolic control [12,22,34]. Additionally, in longstanding diabetes counter-regulation is impaired more frequently and the risk for severe hypoglycaemia increases [35–39]. This notion is in line with the higher number of patients with longstanding diabetes in group $Hypo_{Many}$ and the poor adherence observed in this group if $BG_{act} < BG_{target}$ (see Fig. 1b) as observed in the present study.

Moreover, hypoglycaemia itself affects counter-regulatory responses and promotes hypoglycaemia unawareness due to autonomic failure [40,41]. Therefore, therapy adherence may become more difficult as the duration of diabetes progresses [42]. Patients already have problems integrating therapy algorithms into their daily order and additional unstable metabolic conditions may increase emotional distress, which in turn may contribute to poor adherence [12,43]. The notion that hypoglycaemia is a major factor preventing patients from achieving euglycaemia is corroborated by our finding that mean blood glucose is higher in patients with poor metabolic control ($Control_{Poor}$) as compared to $Control_{Good}$ [26].

In conclusion, in the present study neither the patient nor the diabetologist were aware of the correlation between prescribed and actually applied insulin therapy. Continuous knowledge of individual adherence patterns may eventually benefit overall metabolic control.

Many patients use insulin analogues (basal or rapid acting). As fear of hypoglycaemia is a major reason for decreased adherence, it would be interesting to see whether the use of analogues (known to prevent hypoglycaemia) could increase adherence. These questions could be addressed in a larger, prospective multicentre analysis of treatment adherence over a longer study period.

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