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ORIGINAL ARTICLE

Factors that influence basal insulin requirement in type 2 diabetes

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Abstract In clinical practice, basal insulin dosage (BID) for the treatment for type 2 diabetes given as slow-acting analogues or NPH insulin varies widely when adjusted for body weight (UI/kg). In this study, we investigated the interrelationship between BID and anthropometric, laboratory and clinical parameters. A total of 681 type 2 diabetic patients, treated with bedtime insulin in association with other antidiabetic drugs (preprandial insulin and/or oral agents), were studied. Anthropometric, clinical and biochemical parameters, as well as micro- and macrovascular complications, were evaluated. Non-alcoholic fatty liver disease (NAFLD) was assessed by liver ultrasound. BID was titrated to achieve a fasting blood glucose target of ≤6.7 mmol/L (120 mg/dL). In the multivariate analysis, BID was significantly associated with waist circumference ($p = 0.04$) and the insulin treatment duration ($p = 0.004$) as the type of insulin treatment ("basal-bolus" regimen vs. basal insulin only, $p < 0.0001$), the use of lipid-lowering drugs ($p = 0.0003$) and insulin sensitizers ($p = 0.005$). Several glycometabolic parameters were strongly associated with BID (HbA1c $p = 0.01$, FPG $p < 0.0001$, HDL $p = 0.02$, triglycerides $p = 0.03$). Moreover, the presence of severe NAFLD resulted in a higher BID ($p = 0.03$). We concluded that when starting and titrating the basal insulin in type 2 diabetes, certain anthropometric, laboratory and clinical factors can be useful to find optimal BID more quickly and appropriately.

Keywords Type 2 diabetes mellitus · Basal insulin requirement · Insulin therapy · Metabolic syndrome

Abbreviations

BID	Basal insulin dosage
NAFLD	Non-alcoholic fatty liver disease
MetS	Metabolic syndrome
MDIs	Multiple daily injections
FPG	Fasting plasma glucose
WC	Waist circumference
CVD	Cardiovascular disease
SU	Sulphonylureas
TZD	Thiazolidinediones

Introduction

Treatment for type 2 diabetes with lifestyle changes and oral agents (secretagogues and/or insulin sensitizers and, today, incretin mimetics and DPP-IV inhibitors) is frequently supplemented first with basal insulin [1] (slow-acting analogues or NPH/NPL insulin) and then subsequently replaced by multiple daily injections therapy (MDIs) (±oral insulin sensitizers) when this combined treatment no longer results in satisfactory glycemic control [2]. When a patient begins basal insulin, adequate dosing becomes critical to achieve good glycemic control with minimal risk of hypoglycemia, and a fine titration is needed to ensure its success. Although simple forced titration algorithms for basal insulin exist, on the basis of statements of the target ranges for fasting plasma glucose (FPG) or

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based on patient weight, they appear often suboptimal because basal insulin requirements in type 2 diabetic patients (even with similar values of FPG and weight) can vary enormously from patient to patient. This fact is well known in daily clinical practice and is backed up by many clinical studies in which slow-acting analogues or NPH insulin (in association with oral agents or in basal-bolus regimens) has been used [3–6]. To the best of our knowledge, no extensive clinical studies of type 2 diabetic patients have evaluated the associations between anthropometric, laboratory and clinical variables and the individual basal insulin requirement. We recorded the basal insulin doses, adjusted for weight (BID, UI/kg), of a large group of type 2 diabetic patients treated with slow-acting insulin analogues (glargine or detemir), NPH or NPL insulin (±oral agents or other preprandial insulin). The BID was recorded after titrating to achieve acceptable fasting blood glucose levels. We subsequently studied the relationship between BID and anthropometric, laboratory and clinical parameters.

Patients and methods

Study group

In this observational, cross-sectional study, 681 type 2 diabetic patients admitted to our ward for a poor glycemic control and/or to evaluate micro- and macrovascular complications were recruited consecutively from 01-01-2009 to 31-12-2010; all patients were treated (already receiving or starting in the ward) with a daily bedtime basal insulin treatment (glargine, detemir, NPH/NPL insulin) in association with other antidiabetic drugs (preprandial insulin and/or oral agents). The exclusion criteria were as follows: acute illnesses, renal disease (serum creatinine $\geq$ 133 mmol/L in men and $\geq$120 mmol/L in women), chronic active hepatitis (liver transaminases $\geq$2 times than normal ranges and/or positive serology for viral hepatitis B and C) or glucocorticoid therapy. The medical history of the patients was recorded for reference purposes. After hospital admission, all patients underwent a dietary protocol according to Italian Diabetes Society guidelines [7]. The dosage of basal insulin (analogues, NPH or NPL insulin) was adjusted according to fasting blood glucose levels using a single titration table (as our protocol of clinical care for all diabetic, basal insulin–treated, hospitalized patients) (Table 1). The average length of stay was of 12 ± 4 days. The study protocol was approved by local Ethics Committees.

Table 1 Titration schedule for basal or NPH/NPL insulin

Fasting blood glucose levels (mmol/L) for 2 consecutive days	Adjustment of basal insulin dose (UI)
>10	8
8.9–10	6
7.8–8.8	4
6.7–7.7	2
5.6–6.6	1 or maintain dose
4.4–5.5	maintain dose
3.3–4.3	–2
<3.3	–4

Clinical and laboratory measurements

Body weight was measured in light clothing and without shoes to the nearest half kilogram. Height was measured to the nearest half centimetre. BMI was calculated as weight (kg) divided by height^2 (m). Waist circumference (WC, to the nearest half centimetre) was measured at the midpoint between the lower border of the rib cage and the iliac crest. Arterial blood pressure was taken with a standard mercury blood pressure meter. Three blood pressure readings were obtained at 1-min intervals, and the second and third systolic and diastolic pressure readings were averaged and used in the analysis. Blood was taken from all patients after fasting 10–12 h from their admission to the ward. All biochemical parameters were evaluated by standard laboratory procedure. All patients were tested for viral hepatitis B and C. LDL cholesterol was calculated by the Friedewald formula, except for serum triglyceride concentration >400 mg/dL. HbA1c was measured by a high-performance liquid chromatography analyzer (HPLC); the upper limit of normal for the laboratory was 5.9%. During their stay in hospital, we performed a daily glycemic profile with 6 finger-prick tests (One Touch Ultra, LifeScan, Milpitas, California, USA) on all patients. Microvascular (fundus oculi and/or fluorescence angiography, urinary albumin excretion, 10-g monofilament test and vibration perception threshold analysis) and macrovascular (electrocardiogram, echocardiography, echo-Doppler scanning of carotid and lower limb arteries) complications were studied, as was the presence and severity (by liver ultrasound) of non-alcoholic fatty liver disease (NAFLD).

Definition of terms

Metabolic Syndrome (MetS) was diagnosed using the AHA-NHLBI criteria [8] by the presence of diabetes and $\geq$2 of the following components: (1) WC $\geq$ 102 cm in men and $\geq$88 cm in women; (2) triglycerides $\geq$ 1.7 mmol/L (150 mg/dL), or fibrates/fish oil users; (3) HDL $<$ 1.0 mmol/L (40 mg/dL) in men and <1.29 mmol/L (50 mg/dL) in women; and (4) blood pressure $\geq$ 130/85 mmHg, or receiving treatment. The severity of NAFLD was determined by a semiquantitative scale in which the patients

were subdivided into 3 categories: grade 0 (absence of steatosis) = normal echogenicity; grade 1 (mild–moderate/moderate steatosis) = diffuse increases in fine echoes in liver parenchyma, with normal visualization of diaphragm and intrahepatic vessel borders and exaggeration of liver and kidney echo discrepancy; and grade 2 (moderate–severe/severe steatosis) = marked increase in fine echoes with poor or non-visualization of the intrahepatic vessel borders, diaphragm, and posterior right lobe of the liver, and larger discrepancy between hepatic and renal echoes. Microalbuminuria was defined as a urinary albumin excretion level between 30 and 299 mg/day on at least two of three occasions. Diabetic retinopathy was defined as any retinal injury linked to diabetes. Diabetic peripheral neuropathy was diagnosed on the basis of neuropathic symptoms, insensitivity to a 10-g monofilament and abnormal current perception threshold. Cardiovascular disease (CVD) was defined as one or more of the following pathologies: history of myocardial infarction, previous procedures of revascularization (coronary balloon angioplasty, stent or artery bypass surgery), evidence of clinically significant myocardial ischemia, previous unstable angina, stable angina with established coronary artery disease (angiogram ≥50% stenosis in major artery or positive stress test), previous transient ischemic attacks, previous stroke, previous carotid thromboendarterectomy, carotid stenosis ≥70% as diagnosed by echo-Doppler scanning or peripheral vascular disease (history of intermittent claudication or rest pain as confirmed by echo-Doppler scanning, prior peripheral revascularization procedures, amputation of lower limbs).

Statistical analysis

Descriptive summary statistics were generated for the study group using mean ± SD for continuous variables and proportions for nominal variables. If necessary, logarithmic transformation was performed to achieve a normal distribution. Simple regression analyses were used to evaluate the associations between BID and each variable of interest. Multivariate regression analyses were performed with BID as the dependent variable to evaluate the independent contributions of age, gender, BMI, waist circumference, diabetes and insulin treatment duration, FPB, triglycerides, HDL cholesterol, HbA1c, SBP, DBP, type of insulin therapy (basal-bolus or only basal insulin and hypoglycemic drugs), use of insulin sensitizers, antihypertensive and lipid-lowering drugs, hepatic steatosis and micro- and macrovascular complications. The χ^2 test was applied to test the differences between categorical variables. A p value less than 0.05 was considered statistically significant. All analyses were performed by Statistical package, SPSS version 16 (Chicago, IL, USA) and StatView (version 5.01; SAS Institute, Cary, NC).

Results

Clinical and biochemical characteristics of the patients are presented in Table 2. The average age of the patients was 65 ± 10.5 years, BMI was 31.6 ± 6.5 kg/m^2 and diabetes duration was 17 ± 10 years; HbA1c on admission was 9.2 ± 1.9%, with FPG of 12.1 ± 4.4 mmol/L. In total, 180 (26.4%) patients were treated with basal insulin and oral blood glucose–lowering medication [sulphonylureas (SU) or glinides and/or metformin ± thiazolidinediones (TZD)] and 501 patients (73.6%) were treated with a basal-bolus regimen (±metformin ± TZD). Metformin (and/or TZD) treatment was undertaken by 350 patients (51.4%). Overall, 451 patients (66.2%) used glargine, 143 (21%) detemir, 50 (7.3%) NPL and the remaining 37 (5.4%) NPH.

Insulin requirement and anthropometric/clinical data

A significant association was observed between BID and waist circumference ($p < 0.05$). BMI and age, however, were not significantly associated with BID ($p = 0.22$ and 0.12, respectively). No association with BID was found for SBP and DBP ($p = 0.58$ and 0.67, respectively), although 79% of the group was already being treated for hypertension. BID was significantly associated with both the duration of diabetes and the duration of insulin treatment ($p = 0.0004$ and < 0.0001, respectively). Female patients used greater amounts of daily basal insulin than male patients (0.267 vs. 0.235 UI/kg $p = 0.001$).

Insulin requirement and metabolic parameters

BID was significantly associated with several glycometabolic parameters: HbA1c ($p < 0.0001$), FPG ($p < 0.0001$), triglycerides ($p < 0.0001$) and HDL cholesterol ($p = 0.01$). We found a significant difference, in terms of BID, between patients diagnosed with MetS and those without MetS (0.26 vs. 0.22 UI/kg, $p = 0.005$); there was evidence of a "*continuum*" when the patients were divided into four groups according to the number of positive diagnostic criteria for MetS (from 1 to 4) (Fig. 1).

Insulin requirement and NAFLD

All patients underwent a liver echo-scan by a single operator. A diagnosis of steatosis was made on the basis of altered echotexture (see "Definition of terms"). When the steatosis was divided into two levels of severity (grade 1 and 2), a significant difference in insulin requirement was noted between the group of patients with an absence of steatosis (grade 0) and those with moderate to severe steatosis (grade 2, $p < 0.05$).

Table 2 Clinical and metabolic parameters of patients (all patients and grouped according to gender)

Variables	Whole group	Men	Women	*p* value
N (%)	681	324 (47.6)	357 (52.4)	
Age (years)	65.1 (10.5)	63.3 (10)	66.8 (9.8)	<0.0001
Weight (kg)	81.1 (17.4)	84.8 (17.5)	77.8 (16.6)	<0.0001
BMI (kg/m^2)	31.6 (6.5)	30.3 (5.8)	32.8 (6.8)	<0.0001
CV (cm)	106.5 (16.4)	104.1 (15.3)	108.7 (17.1)	0.0009
Diabetes duration (years)	17.1 (10.1)	16.4 (10.7)	17.8 (9.9)	NS
FPG (mmol/L)	12.1 (4.4)	12.2 (4.3)	12.1 (4.5)	NS
HbA1c (%)	9.2 (1.9)	9.2 (2.0)	9.2 (1.8)	NS
HDL cholesterol (mmol/L)	1.21 (0.36)	1.11 (0.33)	1.28 (0.35)	<0.0001
Triglycerides (mmol/L)	1.76 (1.1)	1.78 (1.2)	1.74 (1.0)	NS
Systolic blood pressure (mmHg)	132.1 (15.5)	131.3 (15.1)	132.8 (15.9)	NS
Diastolic blood pressure (mmHg)	76.3 (9.1)	76.5 (8.6)	76.1 (9.5)	NS
AHA-NHLBI–defined metabolic syndrome (%)	542 (79.6)	225 (69.4)	317 (88.8)	<0.0001
Only basal insulin (±oral secretagogues ± oral insulin sensitizers) (%)	180 (26.4)	93 (28.7)	87 (24.4)	NS
Basal-bolus therapy (±metformin)	501 (73.6)	231 (71.3)	270 (75.6)	NS
Basal insulin: detemir, glargine, NPL, NPH (%)	21, 66, 7, 5	21, 67, 7, 5	21, 66, 8, 5	NS
Metformin users (%)	350 (51.4)	158 (48.8)	192 (53.8)	NS
Antihypertensive drug users (%)	78.9	71.9	85.2	<0.0001
Lipid-lowering drug users (%)	55.9	54.6	57.1	NS
Current smokers (%)	16.4	25	9	<0.0001

Mean ± SD shown. Analysis was performed by one-way ANOVA or the χ^2-test for continuous and categorical variables, respectively. *NS* not significant

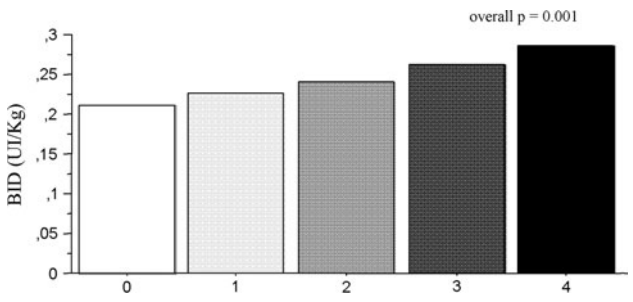

Fig. 1 BID (UI/kg/die) and the presence of diagnostic criteria of MetS (0–4)

Insulin requirement and diabetic complications

Of the 681 patients, 335 (49.2%) had previous CVD; 96 of these (28.7%) were classified as having cerebrovascular disease; 89 (26.6%) as having cardiovascular disease; 56 (16.7%) with peripheral vascular disease; and the remaining 94 (28%) with polyvascular atherosclerotic disease. We found no difference in terms of BID between patients with or without macrovascular complications ($p = 0.14$, adjusted for age and glycemic control). Even when patients were divided into four subgroups of vascular disease (1-cerebrovascular disease, 2-cardiovascular disease, 3-peripheral vascular disease, 4-polyvascular atherosclerotic disease), we found no difference between the groups or between single groups and patients without cardiovascular disease. We also analyzed the relationship between BID and the presence of microvascular complications. We found no significant association between BID and the positive presence of microalbuminuria and of diabetic neuropathy. The presence of diabetic retinopathy was, however, associated with the dosage used ($p = 0.001$).

Insulin requirement and treatment with metformin (and/or TZD)

We noted that in patients treated with metformin (and/or TZD), BID was reduced by 14% (0.235 vs. 0.274 IU/kg, $p < 0.0001$).

Insulin requirement and type of insulin regimen (only basal or MDI)

Of the 681 patients studied, 501 (73.6%) were treated with MDI (basal-bolus regimen ± insulin sensitizers), and the remaining 180 (26.4%) were treated with a single dose of

insulin associated with oral blood glucose–lowering medication (secretagogues and/or insulin sensitizers). We observed a significant difference in BID (0.278 vs. 0.178 $p < 0.0001$) between these two groups of patients. In total, 451 patients (66%) were treated with glargine, and 143 (21%) were treated with detemir (both used in a single evening dose). The titrating algorithm for both basal analogues was the same (Table 1). The FPG target was reached, in most of the patients, approximately 6 days (±3) after admission. We did not find any difference in BID between the two analogues (0.260 UI/kg of glargine versus 0.268 UI/kg of detemir, $p = 0.49$). As the number of patients treated with NPL and NPH was so small, these patients were excluded from this analysis.

Multivariate analyses

Using multiple regression analysis, we observed a significant and independent association between basal insulin requirement and the following parameters: gender ($p = 0.0002$), waist circumference ($p = 0.04$), insulin treatment duration ($p = 0.004$), basal-bolus therapy ($p < 0.0001$), treatment with insulin sensitizers ($p = 0.005$) and lipid-lowering drug therapy ($p = 0.0003$), HbA1c ($p = 0.01$), FPG ($p < 0.0001$), HDL ($p = 0.02$), triglycerides ($p = 0.03$) and presence/severity of NAFLD ($p = 0.03$) (Table 3).

Table 3 Multiple regression analysis

Dependent variable: basal insulin requirement			
Independent variables	Regression coefficient	SE	*p*
Gender	−0.048	0.013	**0.0002**
Age	−0.001	0.001	0.0852
BMI	−0.002	0.001	0.2613
Waist circumference	−0.001	0.001	**0.0421**
FPG	4.6×10^{-4}	9.4×10^{-5}	**<0.0001**
HDL	−0.001	4.6×10^{-4}	**0.0222**
Triglycerides (log-transformed)	0.061	0.028	**0.0295**
HbA1c	0.010	0.004	**0.0104**
Systolic blood pressure	4.6×10^{-4}	4.8×10^{-4}	0.3366
Diastolic blood pressure	1.7×10^{-4}	0.001	0.8293
Diabetes duration	3.4×10^{-4}	0.001	0.6464
Insulin treatment duration	0.003	0.001	**0.0038**
Basal-bolus therapy	0.072	0.015	**<0.0001**
Insulin sensitizers	−0.038	0.013	**0.005**
Antihypertensive drug	0.010	0.018	0.5811
Lipid-lowering drug	0.044	0.012	**0.0003**
Hepatic steatosis	0.012	0.005	**0.0281**
Microalbuminuria	−0.007	0.013	0.5735
Retinopathy	0.009	0.013	0.4686
Neuropathy	0.002	0.012	0.8870
Macrovascular complications	−0.003	0.012	0.8219

Bold values are statistically significant

Discussion

Over time, the maintenance of good glycometabolic control is often only possible with lifestyle changes to achieve a normal weight, together with a progressive adjustment of pharmacological treatment, which in most cases involves oral drugs in conjunction with insulin treatment when levels of HbA1c can no longer be solely controlled by the former treatment [9]. Appropriate insulin dosage after starting therapy using NPH, NPL or slow-acting analogues (the latter is increasingly used today because of their better pharmacokinetics profile, which avoids night time peaks with consequently less hypoglycemic risk) [10] is crucial to reach the glycemic target level of HbA1c < 7.0%. The starting dose is fixed, and successive adjustments are undertaken in a simple manner according to FPG levels with progressive dose increases made until the blood glucose target is met. Common clinical experience and evidence from diverse random clinical studies in which NPH insulin or slow-acting analogues have been used in the treatment for type 2 diabetic patients show that insulin basal requirement changes profoundly from patient to patient. They usually have severe hepatic and peripheral insulin resistance, often linked to the presence of steatosis. Ryysy et al. [11] have already demonstrated that the difference in basal insulin requirements seems to be mainly linked to the variation in insulin action in the individual, rather than to the variable subcutaneous absorption of the insulin itself. In our study of a large group of type 2 diabetics treated with basal insulin (NPH, NPL or slow-acting analogues), we analyzed the relationship of BID (IU/kg) with the following: clinical features, anthropometric characteristics, laboratory data; components of metabolic syndrome; liver steatosis (evaluated by echo-scan); micro- and macrovascular complications; treatment with insulin sensitizers and lipid-lowering and antihypertensive drugs; the type of insulin treatment used (only basal insulin or basal-bolus therapy). We found no strong association between BMI and BID, confirming that body mass index is a far from reliable means of estimating the level of insulin resistance in single individuals; instead, waist circumference, a well-known marker of insulin resistance, is significantly associated with the insulin requirement. There is no association between age and dosage used, as might have been predicted; however, the longer the period of insulin treatment, the greater the insulin requirement. This finding shows that a progressive reduction in insulin reserves

causes a progressive increase in the insulin requirement. When MetS is diagnosed, it impinges greatly on the insulin requirement; furthermore, when patients were divided into four subgroups according to the number of positive diagnostic criteria, a progressive increase in insulin requirement is noted (see Fig. 1). Glycemic control seems to be of crucial importance when we consider the strong association between FPG and HbA1c and the quantity of insulin administered. The other parameters of MetS (triglycerides and HDL cholesterol) are also closely linked. Our female patients took larger doses of insulin than the male patients; this finding is probably a reflection of the basal differences in terms of BMI and waist circumference (see Table 1), which, however, inevitably lead to a higher level of insulin resistance. With regard to insulin requirement and NAFLD, we did note that when patients with steatosis were divided into two groups, those patients with higher levels of intrahepatic fat needed greater doses of insulin than those with no steatosis. This finding agrees with data showing that the variation in liver fat content influences insulin requirement; it has long been noted that an important association exists between triglycerides in the liver and hepatic insulin resistance [12]. Moreover, it was recently demonstrated that visceral obesity (evaluated by abdominal computed tomography) is a better predictor than generalized obesity for basal insulin requirement [13]. No association was found with micro- and macrovascular complications. Treatment with metformin (and/or TZD) reduced insulin requirement by 14%; this positive effect is consistent with the results of previous studies [14]. Basal-bolus therapy, as well as lipid-lowering drugs, is also significantly correlated with BID. Our study does have its limitations, namely, insulin titration times being too short, which was linked to the limited duration of patient hospitalization (12 ± 4 days), and BID was assessed during permanence in a ward (this makes difficult to extrapolate the results to everyday life). However, objectives for FPG were achieved in the majority of patients by the end of their hospital stay. Our study included patients with poor glycemic control (HbA1c and FPG of 9.2% and 12 mmol/L, respectively, upon admission) that usually require a higher dosage of insulin because of glucotoxicity and lipotoxicity (with worsening of insulin sensitivity as well as insulin secretion) with consequent possible overestimation of BID. Furthermore, hypoglycemic treatment for our patients was strongly heterogeneous since it included patients on basal insulin plus sulphonylureas or glinides and/or metformin $\pm$ TZD, patients on basal-bolus therapy alone and patients on MDIs $\pm$ metformin $\pm$ TZD; however, this "scenario" is representative of "real-life," and just for this reason, type of hypoglycemic therapy (basal-bolus regimen and use of metformin) was considered among the factors to be analyzed making it one among them that most influence BID. International guidelines recommend tight glycemic control to prevent the onset or to reduce the progression of diabetic complications [2]. However, achieving glycemic targets usually represents a major challenge when starting insulin therapy, and a critical point is certainly basal insulin titration. During the last decade, uniform insulin titration algorithms have been applied in several trials initiating long or intermediate acting insulin in type 2 diabetics, often referred to as treat-to-target [15]. Common to all algorithms is that the starting dose is fixed (for example, 10 or 20 UI) or based on weight (0.1–0.2 UI/kg) or on the morning FPG using a simple formula [for example, $(FPG_{mg/dL}\text{-}50)/10$] [16]. However, having considered the enormous heterogeneity of patients, other factors might be considered when estimating the basal insulin dose. In our study, we have demonstrated, in a large group of type 2 diabetic patients, that some anthropometric, clinical and laboratory factors could help to more quickly identify the most appropriate insulin dose for each patient. Although the huge number of independent associations between BID and the many parameters considered could make it difficult to develop a practical guide to physicians for starting basal insulin therapy, maybe we could simplify with a selection of the most significant among them (clinical and laboratory features). The basal insulin starting dose could then be calculated on the basis of individual parameters rather than on a fixed basis or using formulae that take into account only fasting blood glucose or weight. In addition, calculation, on the basis of subjective data, of the insulin basal dose could theoretically help to identify an unusually high insulin requirement and then suggest further diagnostic analysis, which might be able to reveal secondary causes of insulin resistance or a marked secretory failure (e.g., a latent autoimmune diabetes of adult) or provide evidence of unsuccessful patient compliance with therapy.

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Conflict of interest All authors declare that no conflicts of interest are present.

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