Four-Point Preprandial Self-Monitoring of Blood Glucose for the Assessment of Glycemic Control and Variability in Patients with Type 2 Diabetes Treated with Insulin and Vildagliptin

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Received 5 May 2015; Revised 2 October 2015; Accepted 5 October 2015

Academic Editor: Michael Horowitz

The study explored the utility of four-point preprandial glucose self-monitoring to calculate several indices of glycemic control and variability in a study adding the DPP-4 inhibitor vildagliptin to ongoing insulin therapy. This analysis utilized data from a double-blind, randomized, placebo-controlled crossover study in 29 patients with type 2 diabetes treated with vildagliptin or placebo on top of stable insulin dose. During two 4-week treatment periods, self-monitoring of plasma glucose was undertaken at 4 occasions every day. Glucose values were used to assess several indices of glycemic control quality, such as glucose mean, GRADE, M-VALUE, hypoglycemia and hyperglycemia index, and indices of glycemic variability, such as standard deviation, CONGA, J-INDEX, and MAGE. We found that vildagliptin improved the glycemic condition compared to placebo: mean glycemic levels, and both GRADE and M-VALUE, were reduced by vildagliptin ($P < 0.01$). Indices also showed that vildagliptin reduced glycemia without increasing the risk for hypoglycemia. Almost all indices of glycemic variability showed an improvement of the glycemic condition with vildagliptin ($P < 0.02$), though more marked differences were shown by the more complex indices. In conclusion, the study shows that four-sample preprandial glucose self-monitoring is sufficient to yield information on the vildagliptin effects on glycemic control and variability.

1. Introduction

The combination of dipeptidyl peptidase-4 (DPP-4) inhibition with insulin is a glucose lowering strategy for the treatment of type 2 diabetes which has gained considerable interest during recent years [1]. The two treatments have synergistic mechanistic actions [1, 2] and the results of clinical trials show that the combination of DPP-4 inhibition and insulin improves glycemia with low risk of hypoglycemia and prevention of weight gain [3–8]. Whether the combination of DPP-4 inhibition and insulin also minimizes glycemic variability is not completely known but would be important because glycemic variability may contribute to the long-term risk in type 2 diabetes [9–12]. Previous studies on DPP-4 inhibition and glycemic variability typically analyzed the combination with metformin or sulfonylureas [13–18], and not the combination with insulin, when the hypoglycemic drive is stronger. To our knowledge, few studies analyzed glycemic variability in patients under DPP-4 inhibition and insulin, and the study duration was limited to few days [19, 20]. More importantly, however, previous studies on DPP-4 inhibition and glycemic variability assessed only few, basic indices of glycemic variability (typically, the standard deviation of the glycemic values), which only partially and incompletely characterize the glycemic variability.

The aim of this study was to explore the utility of using only 4 preprandial readings per day of blood glucose for the estimation of various indices of glycemic control...
quality and variability, in order to examine whether with
this approach it is possible to verify the improved glycemic
variability by DPP-4 inhibition (vildagliptin) in combina-
tion with insulin. In a recent study we demonstrated that
vildagliptin in combination with insulin reduced glucagon
levels at hyperglycemia and sustained the glucagon coun-
terregulation to hypoglycemia, which yielded lower glucose
levels at hyperglycemia and prevention of hypoglycemia in
type 2 diabetes [21]. In this study, we focused on the char-
acterization of glycemic control quality and variability, and
we also assessed the relation between these indices and the
glycosylated haemoglobin [22]. Of note, it may be clinically
relevant to show that few preprandial glucose readings per
day are sufficient to yield information about the ability of
vildagliptin to improve the glycemic condition, that is, the
levels of both glycemic control and variability. In fact, patients
with type 2 diabetes under insulin therapy typically measure
glycemia preprandially, before insulin administration, and
possibly at bedtime. Thus, it may be important to show that
some information on the glycemic control and variability
can be obtained with such readings only, without the need
of further readings that are usually not taken in the clinical
practice.

2. Materials and Methods

2.1. Subjects. This study utilized data from a single-center
(Lund University), double-blind, randomized, placebo-
controlled crossover study (NCT01219400) in patients with
type 2 diabetes who were treated with a stable dose of
insulin (long-acting insulin (34 ± 16 U) with (n = 22) or
without (n = 7) short-acting insulin (21 ± 13 U)), and with
or without oral hypoglycemic agents, with the primary end
point to examine the glucagon response to insulin-induced
hypoglycemia in these patients [21]. Eligible patients were
18 years or older with a diagnosed antibody-negative type 2
diabetes, a glycosylated haemoglobin (HbA1c) value between
6.5 and 8.5% (48–68 mmol/mol), and fasting plasma glucose
levels (FPG) <15 mmol/L. Patients were excluded if they
were pregnant or lactating, had type 1 diabetes, had acute
infection during the 4 weeks preceding the study, had severe
hypoglycemia within 2 weeks before the study (i.e.,
hypoglycemia which needed assistance of another person),
had severe liver disease, were blood donors, or were treated
with growth hormone or an oral steroid during the 2
months preceding the study. Twenty-nine patients were
eventually enrolled in the study (age = 57.9 ± 1.2 years;
BMI = 30.8 ± 0.8 kg/m²; FPG = 8.6 ± 0.4 mmol/L, HbA1c =
59.9 ± 1.5 mmol/mol, diabetes duration = 14.6 ± 1.6 years).
The daily insulin dose was not significantly changed during
the treatment periods.

2.2. Study Procedure. Each patient attended a screening visit
at week −4, during which inclusion/exclusion criteria were
assessed. Eligible patients were randomized at visit 2 (day
1) and were expected to complete two treatment periods,
receiving a different blinded study medication during each
period (Vildagliptin, Novartis Pharma AG, Basel, Switzer-
land, 50 mg twice a day, or placebo, in random order,
randomized in blocks by the university hospital pharma-
cist). At the baseline (day 1) visit, the study medication
was dispensed for 4 weeks for outpatient treatment. Study
medication was then discontinued, and a 4-week washout
period occurred before the alternative 4-week treatment
period. After each 4-week study period, a hypoglycemia
clamp was undertaken to evaluate glucagon secretion; these
results have been previously reported [21]. During the two 4-
week study periods, self-monitoring of plasma glucose was
undertaken at 4 occasions every day (before breakfast, before
lunch, before dinner, and at bedtime). Samples were taken
through a finger and measured by an AccuCheck glucometer
(Roche, Basel, Switzerland). HbA1c was also taken before
and after the respective 4-week periods. The protocol was
approved by the Ethics Committee of Lund University and
the Swedish Medical Product Agency, and all patients gave
written informed consent before entering the study. The study
was conducted using good clinical practice and in accordance
with the Declaration of Helsinki.

2.3. Calculations. For a detailed analysis of the glucose data,
we assessed several indices of glycemic control quality and
glycemic variability. The indices of glycemic control quality
assess to what extent the glucose data remain near a target
value or in a target range. There are both basic indices of
descriptive statistics and more complex indices. Descriptive
indices include glucose mean, maximum, minimum, 50th
percentile (median), percentage of glucose values in a target
range (3.9–11.1 mmol/L), and below and above a target value
(3.9 and 11.1 mmol/L, resp.). It should be noted that 3.9 and
11.1 mmol/L are arbitrary thresholds, although assumed in
many studies [23]. The more complex indices are as follows:

(i) GRADE (Glycemic Risk Assessment Diabetes Equa-
tion) [24]: glucose values are transformed to yield
a continuous curvilinear response with a minimum
at 5.0 mmol/L and high adverse weighting to hyper-
glycemia and hypoglycemia: GRADE = 425 ×
\[\log_{10}(\text{GluC} \times 30) + 0.16\]², with the glucose value,
GluC, in mmol/L; then, average value is taken.

(ii) M-VALUE (not to be confused with the insulin
sensitivity index from the clamp) [25]: it is a weighted
average of the glucose values, with progressively larger
penalties for more extreme values, thus resulting in
higher values of the index: M-VALUE = [10 ×
\log_{10}(\text{GluC}/\text{IGV})]², where IGV is the ideal glucose
value, typically assumed, as in this study, to be equal
to 6.7 mmol/L; again, average value is then taken.

(iii) Hypoglycemia index [23] is the average of hypo-
glycemic values; if blood glucose value is lower
than a given threshold, the formula for the index
is Hypo index = (LLTR – GluC)².0/30, with GluC
and threshold, LLTR (lower limit of target range), in
mg/dL (typically, LLTR = 4.4 mmol/L).

(iv) Hyperglycemia index [23] is the average of hyper-
glycemic values; if blood glucose value is higher
than a given threshold, the formula for the index is
\[
\text{Hyper}_{\text{index}} = \left(\text{Gluc}_u - \text{ULTR}\right)^{1/30},
\]
with \( \text{Gluc}_u \) and threshold, \( \text{ULTR} \) (upper limit of target range), in
mg/dL (typically, \( \text{ULTR} = 7.8 \text{ mmol/L} \)).

(v) IGC (Index of Glycemic Control) [23] is the sum of
hyperglycemia index and hypoglycemia index.

(vi) LBGI (Low Blood Glucose Index) [26]: it consists in a
transformation that normalizes the blood glucose
scale: \( \text{LBGI} = 1.509 \times \left[10.84 - 5.381\right] \),
for blood glucose values less than 6.2 mmol/L; then,
a risk value is assigned to each blood glucose reading
as follows: \( \text{Risk(LBGI)} = 10 \times \text{LBGI}^2 \); finally, average
value is taken.

(vii) HBGI (High Blood Glucose Index) [26]: similarly to
LBGI, it consists in a transformation that normalizes
the blood glucose scale, for blood glucose values
higher than 6.2 mmol/L: the expression of HBGI is the
same as for LBGI;

(viii) ADRR (Average Daily Risk Range) [27]: it is the sum
of LBGI and HBGI, calculated with the minimum
and the maximum glucose value, respectively.

The indices of glycemic variability measure to what extent
data oscillate: the higher the variability, the higher the value
of such indices. Some basic indices of this type are the glucose
standard deviation (SD) and the interquartile range. More
complex indices are as follows:

(i) CONGA (Continuous Overlapping Net Glycemic
Action) [28]: it is the SD of the difference between
values obtained exactly \( n \) minutes apart; typically,
\( n \) is equal to 60 min (or its multiples), but in this
case we performed the analysis over the glucose
data available, despite the fact that the time interval
between consecutive values was typically higher than
one hour.

(ii) J-INDEX [23] is a combination of information from
mean and SD of all glucose values: \( \text{J-INDEX} = 0.001 \times
(\text{mean} + \text{SD})^2 \).

(iii) MAGE (Mean Amplitude of Glycemic Excursion)
[29] is the arithmetic mean of the glycemic excursions
that are greater than one SD; MAGE (pos.) and
MAGE (neg.) consider in particular the positive and
the negative excursions, respectively.

2.4. Statistical Analysis. After testing for normality of indices
values distributions, possible differences in the values of the
indices after vildagliptin and after placebo were assessed
by nonparametric Wilcoxon Signed Rank Test. \( P < 0.05 \)
was considered statistically significant. Possible relationships
between variables were assessed by linear regression analysis.
Values are reported as mean \( \pm \) SE.

3. Results

The average glucose pattern during the day (before breakfast,
before meal, before dinner, and at bedtime) with vildagliptin
and with placebo when compiled together for all days is
reported in Figure 1. It is seen that vildagliptin reduced
glucose levels throughout the day. This was accompanied by
a reduction in HbA1c with vildagliptin by \(-0.5 \pm 0.1\%\) (\(-4.7\pm
0.6 \text{ mmol/mol}\); \( P < 0.001 \)) whereas, during treatment with
placebo, there was no significant change in HbA1c (change
by \(-0.1 \pm 0.1\%\) \([-1.1 \pm 0.6 \text{ mmol/mol}]\)).

The values of the indices of both glycemic control quality
and glycemic variability, as defined earlier, are reported
in Table 1. Vildagliptin improved the glycemic condition
compared to placebo. Mean (and median) and maximum
glycemic levels were reduced with vildagliptin, whereas
the minimum value, typical of hypoglycemia, remained
unchanged. Vildagliptin also reduced the percentage of
values over 11.1 mmol/L (and this is also confirmed by the
hyperglycemia index), whereas the percentage of values in the
target range (3.9–11.1 mmol/L) appears to be not significantly
changed. As regards the low glycemic values (<3.9 mmol/L),
vildagliptin and placebo showed again similar behavior.
Furthermore vildagliptin tended to reduce the hypoglycemia
index (lower value compared to placebo), though statisti-
cal significance was not reached. GRADE and M-VALUE
showed that vildagliptin increased the glucose values near
the respective target value, that is, 5.0 and 6.7 mmol/L (again,
lower values compared to placebo); the higher value of LBGI
and the lower value of HBGI consistently confirmed the
glucose lowering effect of vildagliptin, also further confirmed
by ADRR. The indices of glycemic variability consistently
showed an improvement of the glycemic condition with
vildagliptin, with values that were all significantly reduced,
except for the interquartile range, where the difference did
not reach statistical significance.

Both with vildagliptin and placebo, there was a weak
but significant relationship between HbA1c after treatment
and glucose mean during the 4-week treatment (\( R = 0.57, \)
4. Discussion

In this study, we show that glycemic control and variability as estimated by several indices on 4-point preprandial self-monitoring of blood glucose (SMBG) is improved during the course of the treatment with vildagliptin add-on to insulin therapy. In fact, the great majority of indices showed a significant amelioration with vildagliptin compared to placebo. In particular, the indices showed that vildagliptin reduced glycemia without increasing the risk for hypoglycemia, which is a clinical experience with vildagliptin added to insulin [2, 3]. In fact, the minimum glucose value was not different between vildagliptin and placebo, suggesting reduction of glucose without increased hypoglycemia risk. This conclusion is strengthened by the hypoglycemia index, which was again not different between the groups. The improvement of glycemic variability by vildagliptin was probably related to its mechanism of action: to reduce glucagon at hyperglycemia and sustain glucagon counterregulation [2, 21]. Of note, some indices, both for glycemic control and glycemic variability, would remain significantly improved with vildagliptin even after the conservative Bonferroni correction for multiple statistical comparisons.

In previous studies, it has been shown that DPP-4 inhibitors improve glycemic variability when added to metformin, although only few indices (typically SD) were evaluated [13–18]. In the study by Mori et al., it was shown that adding sitagliptin to insulin narrowed the range of 24 h glucose fluctuations [19]. We confirm here that these indices were reduced by vildagliptin when added to insulin. Strength of this study was the crossover design and the use of several indices which better characterize the glucose patterns even with only 4 points. Of note, previous studies showed that glycemic variability can in fact be reliably assessed by SMBG, even with few points per day [30, 31]. Specifically, in the study [30], an average of 4.84 samples/day was collected (range 3–7), whereas in the study [31] 70 samples were taken over a period of 4 weeks, thus in line with the number of samples of our study (112 samples over the 4 weeks period).

### Table 1: Indices of glycemic control quality and glycemic variability in patients with type 2 diabetes after placebo and after vildagliptin (data are mean ± SE). For the explanation of the various indices see the Methods section.

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Vildagliptin</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td><strong>Indices of glycemic control quality</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mean (mmol/L)</td>
<td>8.11 ± 0.25</td>
<td>7.36 ± 0.23</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Maximum (mmol/L)</td>
<td>16.37 ± 1.80</td>
<td>13.54 ± 0.66</td>
<td>0.007</td>
</tr>
<tr>
<td>Minimum (mmol/L)</td>
<td>3.76 ± 0.20</td>
<td>3.66 ± 0.19</td>
<td>0.37</td>
</tr>
<tr>
<td>50th percentile (median) (mmol/L)</td>
<td>7.82 ± 0.25</td>
<td>7.13 ± 0.24</td>
<td>0.0001</td>
</tr>
<tr>
<td>Percentage below target (3.9 mmol/L) (%)</td>
<td>2.0 ± 0.6</td>
<td>3.1 ± 0.9</td>
<td>0.055</td>
</tr>
<tr>
<td>Percentage in target (3.9–11.1 mmol/L) (%)</td>
<td>86.1 ± 2.4</td>
<td>89.8 ± 2.2</td>
<td>0.062</td>
</tr>
<tr>
<td>Percentage above target (11.1 mmol/L) (%)</td>
<td>11.9 ± 2.3</td>
<td>7.0 ± 2.0</td>
<td>0.002</td>
</tr>
<tr>
<td>GRADE (unitless)</td>
<td>6.61 ± 0.59</td>
<td>5.17 ± 0.52</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>M-VALUE (unitless)</td>
<td>6.22 ± 1.18</td>
<td>4.97 ± 0.95</td>
<td>0.004</td>
</tr>
<tr>
<td>Hypoglycemia index (unitless)</td>
<td>7.67 ± 1.45</td>
<td>5.66 ± 0.78</td>
<td>0.003</td>
</tr>
<tr>
<td>Hyperglycemia index (unitless)</td>
<td>1.97 ± 0.20</td>
<td>1.61 ± 0.20</td>
<td>0.002</td>
</tr>
<tr>
<td>IGC (unitless)</td>
<td>9.81 ± 1.32</td>
<td>7.32 ± 1.04</td>
<td>0.059</td>
</tr>
<tr>
<td>LBGI (unitless)</td>
<td>0.64 ± 0.15</td>
<td>1.03 ± 0.20</td>
<td>0.002</td>
</tr>
<tr>
<td>HBGI (unitless)</td>
<td>4.57 ± 0.66</td>
<td>3.12 ± 0.56</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ADRR (unitless)</td>
<td>45.0 ± 7.3</td>
<td>35.5 ± 3.8</td>
<td>0.043</td>
</tr>
<tr>
<td><strong>Indices of glycemic variability</strong></td>
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<tr>
<td>Standard deviation (mmol/L)</td>
<td>2.27 ± 0.21</td>
<td>2.00 ± 0.17</td>
<td>0.015</td>
</tr>
<tr>
<td>Interquartile range (mmol/L)</td>
<td>2.87 ± 0.24</td>
<td>2.68 ± 0.26</td>
<td>0.092</td>
</tr>
<tr>
<td>CONGA (mmol/L)</td>
<td>3.12 ± 0.29</td>
<td>2.71 ± 0.22</td>
<td>0.011</td>
</tr>
<tr>
<td>J-INDEX (10^{-3} (mmol/L)^2)</td>
<td>0.12 ± 0.01</td>
<td>0.09 ± 0.01</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MAGE (mmol/L)</td>
<td>4.80 ± 0.48</td>
<td>4.16 ± 0.33</td>
<td>0.010</td>
</tr>
<tr>
<td>MAGE (pos.) (mmol/L)</td>
<td>4.82 ± 0.48</td>
<td>4.20 ± 0.32</td>
<td>0.020</td>
</tr>
<tr>
<td>MAGE (neg.) (mmol/L)</td>
<td>4.77 ± 0.47</td>
<td>4.13 ± 0.35</td>
<td>0.007</td>
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</table>

P = 0.001, and R = 0.52, P = 0.004, resp.). Significant relationships with HbA1c after treatment were also found for glucose median, GRADE, M-VALUE, hyperglycemia index, and HBGI, with typically stronger relationship in vildagliptin (R = 0.47–0.61, P = 0.01–0.0004 for vildagliptin, R = 0.42–0.56, P = 0.02–0.002 for placebo, resp.). Percentage in target index showed a significant inverse relationship with HbA1c after treatment (R = 0.50, P = 0.006 for vildagliptin, R = 0.51, P = 0.004 for placebo). We found also that every index of glycemic variability was related to HbA1c after treatment (R between 0.49 and 0.63, P < 0.007 with vildagliptin, and R between 0.39 and 0.51, P < 0.038 with placebo; see Figure 2).
The assessed indices were grouped into two different categories, that is, indices of glycemic control quality and indices of glycemic variability, although for some indices such division may be arbitrary and some indices may belong to both categories. In fact, for a detailed analysis of repeated glucose data, it is important to evaluate a sufficiently wide battery of indices of both glycemic control quality and glycemic variability. In a given population, some of these indices may show similar results; thus the calculation of all of them may be redundant, but this is not always the case. In fact, many of the indices, which were evaluated in this study, have specificities that may provide peculiar information, since each index weights the different glucose values differently. For example, one index may disclose subtle differences in the glycemic condition between two populations that are not disclosed by other indices. In fact, Rodbard claimed that different indices may have different abilities to detect responses to therapeutic interventions [23]. In more detail, regarding the indices of glycemic control quality, some indices predominantly assess low glucose values (glucose minimum, percentage below target, hypoglycemia index, and LBGI), whereas other indices predominantly assess high glucose values (glucose maximum, percentage above target, hyperglycemia index, and HBGI). Furthermore, other indices focus on euglycemia (percentage in target) and, finally, other indices combine these three facets of the glycemic condition (glucose mean and median, GRADE, M-VALUE, IGC, and ADRR). Among the indices addressing a specific aspect of glycemia, there are some relevant differences: as an example, the M-VALUE, with the ideal glucose value, IGV, equal to 6.7 mmol/L (as used in this study) assigns equal penalty (i.e., the index assumes the same value) for 3.3 mmol/L and 13.3 mmol/L; as regards GRADE, it assigns equal penalty to 2.8 mmol/L and 11.9 mmol/L. Even the indices of glycemic variability do not always provide the same results. For instance, it is claimed that J-INDEX may be relatively insensitive to variations in the low glucose range [23].

It should be noted that the percentage in target index did not reach statistically significant difference between adding vildagliptin or placebo to ongoing insulin therapy. This may be due to the lack of postprandial glucose readings. However, though the percentage in target index was not significantly different between vildagliptin and placebo, all the other indices (except IGC) were significantly different, in some cases also displaying very low P values (such as GRADE: see Table 1). This suggests the importance of assessing several indices, and especially those more complex, for a complete evaluation of the glycemic condition. The importance of assessing several indices is also confirmed by some results of the glycemic variability indices: in fact, the simple, basic interquartile range index failed to display a significant difference between vildagliptin and placebo, whereas all the other indices were significantly different. Moreover, it should be noted that more markedly significant differences were displayed by the more complex indices (J-INDEX, CONGA, and MAGE), thus underlying the potential advantages of such indices compared to the simplest indices. Of note, in this study, the glycemic variability index showing the most marked difference between vildagliptin and placebo was J-INDEX, despite the fact that in previous studies it was reported to be relatively insensitive [23]. This further suggests that the use of a wide battery of indices may be beneficial for accurate and reliable analyses of the glycemic patterns.

We also assessed possible relationships between HbA1c and glucose values. In fact, it is known that in type 2 diabetes HbA1c is related to glucose values, even when glucose values are self-monitored [32]. We found that there was a significant relationship between HbA1c after treatment and the glucose mean of the 4-week period, though the relationship was relatively weak. Possible explanation is that our glucose values were referred to a period of 4 weeks only, whereas it is well known that HbA1c is related to glucose values of longer periods. Furthermore, since it has been postulated that glycemic variability may contribute to glycation [33], we also...
assessed possible relationships between HbA1c and glycemic variability indices. We found that the relationship exists with any index, both with vildagliptin and placebo; yet it appeared that the relationships were stronger with vildagliptin than with placebo.

In this study, we aimed to show that few, preprandial glycemic readings are adequate to assess the glycemic control and variability in patients with type 2 diabetes, which were under insulin and vildagliptin treatment. In fact, the used protocol has some advantages: first, it allowed the assessment of the specific effect of vildagliptin on the fasting, or at least preprandial, glycemic condition; furthermore, such protocol limited the discomfort to the patients, requiring few measurements per day, which are already typically taken in such kind of patients. Thus, we showed that even few glucose samples, not requiring specific medical instrumentation (such as devices for continuous glucose monitoring), or additional self-monitoring glycemic readings (compared to those typically performed in insulin treated patients with type 2 diabetes), are sufficient to provide relevant information on glycemic control and variability: in fact, improvements in glycemic control and variability due to vildagliptin can be observed even when postprandial excursions are not determined. Of course, including postprandial readings may show even more marked differences in glycemic control or variability due to vildagliptin, but in this study our priority was detecting significant vildagliptin effects with minimal requirements in terms of glycemic readings, for easier applicability in the clinical practice. It should also be noted that, similarly to our study, previous studies were in fact focused on the assessment of glycemic variability limited to fasting values [34–38].

5. Conclusions

With the assessment of several indices of glycemic control quality and glycemic variability, we comprehensively evaluated the glycemic condition of patients with type 2 diabetes that underwent vildagliptin treatment in addition to insulin, which is a combination only partially investigated in previous studies. The study showed that there is a clear improvement of both glycemic control quality and glycemic variability after only 4 weeks of vildagliptin therapy.

The study underlines that it is important to compute several indices to evaluate daily glucose levels and fluctuations, since not all indices have similar ability to show possible differences in the glycemic control and variability condition.

Furthermore, the study showed that a simple protocol, requiring few self-monitoring preprandial readings, is sufficient to disclose some significant effects of vildagliptin on glycemic control and variability. It will be of interest to apply similar methodologies to future comparative studies involving two active drugs in combination with insulin.

Conflicts of Interests

Bo Ahren has consulted for Novartis, GlaxoSmithKline, Merck, Sanofi, Novo Nordisk, Boehringer Ingelheim, and Takeda and has received lecture fees from Novartis, Merck, Novo Nordisk, Sanofi, Bristol Myers Squibb, AstraZeneca, and GlaxoSmithKline which all are companies producing DPP-4 inhibitors or GLP-1 receptor agonists. Anja Schweizer is an employee of and holds stock in Novartis. James E. Foley is an employee of and holds stock in Novartis. Andrea Tura, Johan Farngren, and Giovanni Pacini have no relevant conflict of interests to disclose.

Acknowledgment

The authors wish to thank Dr. Andrea Mari for his comments and suggestions.

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