Six-month exenatide improves HOMA hyperbolic product in type 2 diabetic patients mostly by enhancing beta-cell function rather than insulin sensitivity

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Abstract

Objective. – This study aimed to determine whether or not the improvement of glycaemic control with 6-month exenatide therapy in type 2 diabetic patients with secondary failure to combined oral therapy is related to amelioration of β-cell function and/or insulin sensitivity and their combined product.

Research design and methods. – Thirty-three patients with type 2 diabetes were investigated. Their β-cell function and insulin sensitivity were measured using Homeostasis Model Assessment [HOMA-B, HOMA-S and HOMA hyperbolic product (BxS)]. Additional endpoints included changes in weight, HbA1c and plasma adiponectin, as well as baseline clinical and biological characteristics, as potential predictors of HbA1c response.

Results. – After 6 months, unadjusted HOMA-B increased from 33 ± 24% to 43 ± 23% (P = 0.0210), whereas there was no significant change in HOMA-S (from 58 ± 35% to 61 ± 40%). The hyperbolic product increased by a relative 70% (from 15 ± 7% to 22 ± 15%; P = 0.0055). Body mass index decreased from 32.2 ± 5.1 kg/m² to 31.0 ± 4.8 kg/m² (P < 0.0001) and HbA1c from 8.8 ± 1.0% to 7.6 ± 1.2% (P < 0.0001). No change was observed in adiponectin concentrations. Higher baseline HbA1c values were a significant predictor of therapeutic response.

Conclusion. – Exenatide significantly increased HOMA-B and hyperbolic product over a 6-month treatment period with no overall change in insulin sensitivity, despite weight loss. Thus, improved β-cell function rather than increased insulin sensitivity accounts for the bulk of HbA1c reduction following 6 months of exenatide treatment.

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Keywords: Exenatide; β-cell function; Insulin resistance; Hyperbolic product; Glycaemic control

Résumé

Un traitement par exenatide pendant six mois augmente le produit hyperbolique HOMA essentiellement par une amélioration de la fonction B.

Objectifs. – Nous avons voulu déterminer, chez des diabétiques de type 2 en échec d’une bithérapie orale maximale, si l’amélioration du contrôle glycémique observée après six mois de traitement par exenatide était associée à un gain de fonction β-cellulaire et/ou de sensibilité à l’insuline et de leur produit hyperbolique combiné.


Résultats. – Après six mois, le HOMA-B s’est majoré de 33 ± 24 à 43 ± 23% (P = 0.0210), alors qu’il n’y avait pas de changement de HOMA-S (de 58 ± 35 à 61 ± 40%). On observait une augmentation relative du produit hyperbolique de 70% (de 15 ± 7 à 22 ± 15%; P = 0.0055). L’indice de masse corporelle a diminué de 32.2 ± 5.1 kg/m² à 31.0 ± 4.8 kg/m² (P < 0.0001) et l’HbA1c de 8.8 ± 1.0 à 7.6 ± 1.2% (P < 0.0001). Nous n’avons pas objectivé de changement des taux d’adiponectine. Une valeur d’HbA1c plus élevée au départ était un facteur prédictif de réponse au traitement.

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1. Introduction

Hyperglycaemia in type 2 diabetes is the result of progressive failure of β-cell function (BCF) over time, potentiated by concomitant insulin resistance in peripheral tissues [1]. Exenatide, a glucagon-like peptide-1 (GLP-1) receptor agonist, is a synthetic exendin-4, with a half-life of 2.4 hours, that improves glycaemic control as well as BCF markers [2–5]. However, latent improvement in BCF was mostly reported in an acute setting, with exenatide administered on evaluation day, thereby introducing a potential confounder bias as a result of acute glucagon suppression at the time of modelling [6]. In contrast, there is a scarcity of published data on the potential effect of chronic suppression at the time of modelling [6]. In contrast, there is a scarcity of published data on the potential effect of chronic GLP-1 receptor activation by exenatide on BCF and insulin sensitivity assessed following short-term discontinuation of therapy. Therefore, the aim of the present study was to determine, in type 2 diabetic patients with secondary failure to combined oral therapy, whether or not besides improvement in glycaemic control the addition of exenatide for 6 months is associated with improvement in BCF, insulin sensitivity and hyperbolic product 24 hours after discontinuation of the GLP-1 receptor agonist.

2. Research, design and methods

This prospective study was carried out from February 2008 to May 2009 in the outpatients and/or one-day clinic of the Saint-Luc University Hospital (Brussels, Belgium). The recruited subjects were type 2 diabetics, aged 40–80 years, with a body mass index (BMI) of 25–40 kg/m² that was stable over the 3 months prior to inclusion (< 10% variation). One inclusion criterion was a baseline glycated haemoglobin (HbA1c) greater or equal to 7.0% despite a maximum-tolerated combined oral therapy with a BCF stimulant (sulfonylurea or repaglinide) plus metformin. Exclusion criteria included previous or current use of glitazone, systemic glucocorticoids, weight-reducing drug(s) such as sibutramine, or previous exposure to GLP-1 receptor agonists or dipeptidyl peptidase-4 (DPP-4) inhibitors, or any medications that might preclude safe participation in the study.

Informed consent was obtained from all patients. The study was performed in accordance with the Declaration of Helsinki (Belgian registration’s accession number B403200895639; clinicalTrials.gov identifier: NCT00948168).

The following sociodemographic and clinical variables were recorded for every participant: age, gender, known diabetes duration, family history, weight, height, BMI, waist circumference, and blood pressure. At the time of inclusion (T0), patients began exenatide treatment at a dose of 5 μg BID, injected 15 min before meals, for a period of 4 weeks, followed by an increase to 10 μg BID, according to tolerability, for the remainder of the study period (6 months). All patients self-monitored their blood glucose levels, which included daytime profiles at least twice a week (before breakfast, lunch and dinner, and at bedtime). Sulfonylurea/glinide and metformin dosages remained at the inclusion levels over the study period unless patients experienced hypoglycaemic episodes [defined as a blood glucose measurement less than 60 mg/dL (3.4 mmol)]. In such cases, a 50% reduction of the sulfonylurea/glinide dosage was implemented.

Visits took place at T0, after 4 weeks (T1) and after 6 months (T6) of exenatide therapy. At each visit, anthropometric and clinical parameters were measured (at T0 and T6) together with fasting plasma glucose, HbA1c and routine biochemistry, including serum fasting lipids, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyltransferase (γ-GT). Plasma adiponectin was measured at T0 and T6 by radioimmunoassay (RIA) using a commercial kit (Linco Research, St Charles, MO, USA).

Each subject underwent (at T0 and T6) a non-invasive, combined assessment of insulin sensitivity and BCF, using a computer-based version (http://www.dtu.ox.ac.uk/) of Homoeostasis Model Assessment (HOMA-2), from triplicate means of fasting glucose, and specific insulin levels obtained after overnight fasting and discontinuation of glucose-lowering or glucose-sensitizing therapies for 24 hours (or 48 hours for long-acting sulfonylureas) [7,8]. Values of HOMA-B (%) were plotted as a function of HOMA-S (%), thereby defining a HOMA product area [(BxS)%, normal value 100%], as reported elsewhere [9]. Age-standardized (BxS) deficit (%/year) was obtained by dividing 100 – (BxS) by the patient’s age [10].

Adverse events were assessed at each visit, and patients were allowed to withdraw from the study if they had unacceptable side effects due to the medication or other personal reasons.

The primary objective of the study was to evaluate changes in HbA1c and HOMA determinants [HOMA-B – S – (BxS)] over 6-month exenatide therapy. The secondary endpoints included body weight and waist circumference changes between baseline and after 6 months of exenatide. Also analyzed were baseline clinical and HOMA characteristics as predictors of HbA1c response (responders defined as belonging to the above-median value for ΔHbA1c T6 – T0 vs those less-responsive/non-responders to 6-month exenatide therapy) and treatment tolerability.

Results are presented as means ± 1 standard deviation (SD) or as proportions. The significance of the differences between means was assessed by Student’s t test or, alternatively, by Welch’s test for datasets with significant differences in SDs, and by Fisher’s exact test for differences in proportions. Results were considered significant or non-significant (NS) at \( P < 0.05 \), respectively.
3. Results

The study cohort included 33 patients (male-to-female ratio: 55:45) who received, from T0 onwards, subcutaneous exenatide BID in addition to their current glucose-lowering dual therapy. Age and known diabetes duration were 60 ± 10 years and 10 ± 9 years, respectively (Table 1). A metabolic syndrome phenotype [American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI) score ≥ 3/5] was present in 31 patients. Mean fasting plasma glucose at T0 was 12.0 ± 2.6 mmol/L and HbA1c was 8.8 ± 1.0%. HOMA-S and HOMA-B values at T0 (after ≥ 24 h withdrawal of all antihyperglycaemic drugs) are presented in Table 2. Baseline HOMA product (BxS) was markedly reduced at T0 (15 ± 7%). Baseline adiponectin was 7.6 ± 2.2 μg/dL.

After 6 months, a modest reduction (−4%) in BMI was observed—from 32.2 ± 5.1 kg/m² to 31.0 ± 4.8 kg/m² (P < 0.0001). Waist circumference decreased from 112 ± 13 cm to 109 ± 13 cm (P = 0.0061). Fasting plasma glucose was significantly reduced to 10.5 ± 2.7 mmol/L (P = 0.0064), and HbA1c was reduced from 8.8 ± 1.0% to 7.6 ± 1.2% (P < 0.0001). Results are expressed as means (1 SD) or proportions (%); LDL: low-density lipoprotein; HDL: high-density lipoprotein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; γ-GT: gamma-glutamyltransferase.

Table 2
Anthropometric and metabolic changes at inclusion (T0) and after 6-month exenatide therapy (T6) in patients with type 2 diabetes.

<table>
<thead>
<tr>
<th></th>
<th>T0</th>
<th>T6</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>kg</td>
<td>kg</td>
<td></td>
</tr>
<tr>
<td>Delta weight</td>
<td>93.2 (18.4)</td>
<td>89.5 (17.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Body mass index (BMI)</td>
<td>kg/m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delta BMI</td>
<td>32.2 (5.1)</td>
<td>31.0 (4.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Waist</td>
<td>cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delta waist</td>
<td>112 (13)</td>
<td>109 (13)</td>
<td>0.0061</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>mmHg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delta systolic BP</td>
<td>139 (17)</td>
<td>131 (14)</td>
<td>0.0032</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>mmHg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delta diastolic BP</td>
<td>78 (12)</td>
<td>79 (11)</td>
<td>NS</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>mmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delta fasting glucose</td>
<td>12.0 (2.6)</td>
<td>10.5 (2.7)</td>
<td>0.0064</td>
</tr>
<tr>
<td>HOMA-S</td>
<td>%</td>
<td>33 (24)</td>
<td>0.0210</td>
</tr>
<tr>
<td>Delta HOMA-S</td>
<td>58 (35)</td>
<td>61 (40)</td>
<td>0.6150</td>
</tr>
<tr>
<td>HOMA-B</td>
<td>%</td>
<td>15 (7)</td>
<td>0.0055</td>
</tr>
<tr>
<td>Delta HOMA-B</td>
<td>33 (24)</td>
<td>43 (23)</td>
<td>0.0210</td>
</tr>
<tr>
<td>HOMA product (BxS)</td>
<td>%</td>
<td>22 (15)</td>
<td>0.0055</td>
</tr>
<tr>
<td>Delta (BxS) (absolute)</td>
<td>15 (7)</td>
<td>7 (14)</td>
<td></td>
</tr>
<tr>
<td>Delta (BxS) (relative)</td>
<td>33 (24)</td>
<td>10 (22)</td>
<td></td>
</tr>
<tr>
<td>HbA1c</td>
<td>%</td>
<td>8.8 (1.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Delta HbA1c</td>
<td>8.8 (1.0)</td>
<td>7.6 (1.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HbA1c &lt; 7.0%</td>
<td>μg/mL</td>
<td>36 (2.3)</td>
<td>0.7950</td>
</tr>
<tr>
<td>Delta adiponectin</td>
<td>7.6 (2.2)</td>
<td>36 (2.3)</td>
<td>0.7950</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>mg/dL</td>
<td>158 (27)</td>
<td>0.0174</td>
</tr>
<tr>
<td>Delta cholesterol</td>
<td>158 (27)</td>
<td>146 (29)</td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>mg/dL</td>
<td>82 (26)</td>
<td>0.0174</td>
</tr>
<tr>
<td>Delta HDL cholesterol</td>
<td>82 (26)</td>
<td>78 (21)</td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>mg/dL</td>
<td>40 (9)</td>
<td>NS</td>
</tr>
<tr>
<td>Delta LDL cholesterol</td>
<td>40 (9)</td>
<td>41 (9)</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>mg/dL</td>
<td>181 (101)</td>
<td>0.0039</td>
</tr>
<tr>
<td>Delta triglycerides</td>
<td>181 (101)</td>
<td>127 (65)</td>
<td></td>
</tr>
</tbody>
</table>

Results are expressed as means (1 SD) or proportions (%); BP: blood pressure; BxS: hyperbolic function; HOMA-S: insulin sensitivity; HOMA-B: beta-cell function from homeostasis model assessment (HOMA).

* Significance of differences between T0 and T6, from paired Student’s t test; NB: lipid modifications are from the 22 patients who remained on stable doses of lipid-lowering agents throughout the study.
HbA1c that was 1.0% lower (8.3 ± 0.8% to 7.6 ± 0.8%).

The present study demonstrates, for the first time in patients with type 2 diabetes with secondary failure to combined oral therapy, that long-term administration of exenatide improves unadjusted BCF as well as BCF adjusted for individual insulin sensitivity, as measured in the fasting state by the HOMA hyperbolic product. These results were observed in non-acute conditions after at least 24 hours discontinuation of all glucose-lowering oral drugs, including exenatide.

A significant improvement in BCF (HOMA-B) assessed in the basal state was clearly observed in the present study. This is all the more remarkable as the phenotype of the type 2 diabetic study participants, in obvious secondary failure to combined oral therapy, was characterized by markedly reduced BCF adjusted for individual insulin sensitivity, as measured in the fasting state by the HOMA hyperbolic product. These results were observed in non-acute conditions after at least 24 hours discontinuation of all glucose-lowering oral drugs, including exenatide.

4. Discussion

The present study demonstrates, for the first time in patients with type 2 diabetes with secondary failure to combined oral therapy, that long-term administration of exenatide improves unadjusted BCF as well as BCF adjusted for individual insulin sensitivity, as measured in the fasting state by the HOMA hyperbolic product. These results were observed in non-acute conditions after at least 24 hours discontinuation of all glucose-lowering oral drugs, including exenatide.

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rable data were reported for liraglutide, another GLP-1 receptor agonist, which has a half-life of 13 hours following subcutaneous administration [17–19]. In all these studies, BCF was, however, not adjusted for any prevailing individual insulin sensitivity.

The improvement in BCF, as demonstrated by the marked rise in (BxS) product, could be the result of lower basal and/or postprandial glucotoxicity linked to overall improved glycaemic control [20]. Less lipotoxicity exerted upon BCF might also be expected from the improved anthropometric data following sustained weight loss and reduction in waist circumference, both suggestive of less overall adiposity and reduced visceral fat following long-term exenatide. On the other hand, GLP-1 was identified as a powerful insulinotropic hormone binding to β-cell GLP-1 receptors. These findings are also in keeping with a series of animal models in which GLP-1 or exenatide were shown to exert trophic effects on pancreatic β-cells while reducing apoptosis [21]. It cannot, therefore, be ruled out that exenatide administration in the present study restored some β-cell mass/functionality lost as part of the natural history of type 2 diabetes. However, this concept is not in agreement with data from Buncic et al. [6], who recently demonstrated that BCF returned to pretreatment values following a 4-week discontinuation of exenatide in type 2 diabetic patients treated for 1 year.

As far as insulin sensitivity is concerned, our data indicate no significant changes in HOMA-S and plasma adiponectin, a systemic insulin-sensitizing adipokine that is down-regulated in many states associated with central fat expansion and insulin resistance [22]. An increase in adiponectin values has been reported in previous studies in which the magnitude of weight loss (at least 10%) [23] was higher than in the present study. Therefore, the absence of adiponectin change was not unexpected in our patients, and it might even be hypothesized that the weight loss in the present study was not sufficient to induce changes in adiponectin [24]. Nevertheless, the absence of HOMA-S modifications in the present study is in agreement with Klonoff et al. [5] as well as of Vella et al. [25] who, on the basis of basal and prandial insulin infusion, considered that GLP-1 had only negligible effects on either insulin action or glucose effectiveness in type 2 diabetic patients. Furthermore, lack of improvement in insulin sensitivity was also reported following liraglutide therapy [18,19]. On the other hand, data obtained from animal studies and a small body of human studies indicate that GLP-1 or exenatide may exert certain insulin-sensitizing effects [6,12,26,27]. The factors underlying such discrepancies have yet to be identified. The apparent insulin-sensitizing effect, if observed, could be the consequence of overall improved glucose control, weight loss and/or a direct effect on major insulin-sensitive target organs. GLP-1 or GLP-1 receptor agonists, by decreasing food intake, could also reduce not only adiposity but also have a negative impact on lean body mass, which could indirectly account for the limited (or lack of) benefit in terms of insulin sensitivity.

As reported in previous studies [2–6], we also observed, in our type 2 diabetes patients poorly controlled by maximum-tolerated oral glucose-lowering agents, that exenatide for 6 months resulted in sustained reductions in fasting plasma glucose and HbA1c levels. This could be the result of improved glucose-dependent BCF, either glucose-sensing or insulin-secretion capacity [22], as well as from reduced postprandial glucose excursions (such as from a reduced gastric-emptying rate) and/or reduced hepatic glucose output in the setting of weight loss or glucagon suppression. In previous studies, exenatide caused smaller reductions in fasting than in postprandial glucose, the drop in HbA1c being therefore mostly ascribed to a sustained reduction in postprandial glycaemia [3], which was not assessed in the present study.

From a clinical standpoint, good responsiveness to treatment in terms of changes in HbA1c was predicted neither by baseline glucose homeostasis determinants such as HOMA parameters, nor by family history of diabetes, baseline anthropometrics or age-adjusted loss in baseline hyperbolic product, a surrogate measure of BCF loss rate [10], responders being solely characterized by a significantly higher baseline HbA1c value at inclusion. This is in concordance with previous studies concerning GLP-1 agonists therapy [3,5,28], and is all the more relevant as patients with elevated HbA1c in secondary treatment failure are often routinely considered for basal or basal-prandial insulin supplementation. Exenatide therapy was also associated with improvements in blood pressure values and lipid profile, especially triglycerides values, as also reported by others [29].

In conclusion, the present study indicate that exenatide improved HbA1c levels after 6 months in type 2 diabetic patients who could no longer achieve glycaemic control with maximum-dose of combined metformin plus sulfonylurea/glinide therapy. Analysis of HOMA components suggests that this is mostly due to improved β-cell function—as shown by improvement in the hyperbolic product—and, to a much lesser extent, because of increased insulin sensitivity. High baseline HbA1c levels did not preclude a satisfactory response to long-term treatment with the GLP-1 receptor agonist, as illustrated by the high proportion of patients achieving target HbA1c levels at 6 months.

Conflict of interest statement

The authors do not have any conflicts of interest to declare.

References


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