Clinical case

**Exenatide improves weight loss insulin sensitivity and β-cell function following administration to a type 2 diabetic HIV patient on antiretroviral therapy**

L’exenatide chez un patient diabétique de type 2 atteint du VIH favorise la perte de poids, améliore la sensibilité à l’insuline et la fonction β-cellulaire sous antirétroviraux

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**Résumé**

L’utilisation des antirétroviraux dans le traitement de l’infection par le virus de l’immunodéficience humaine (VIH) est associée, surtout pour les premières générations, à des effets secondaires comme la lipodystrophie, la stéatose hépatique et l’insulinorésistance, pouvant déclencher un diabète secondaire ou aggraver un diabète existant. L’utilisation du Glucagon-Like Peptide-1 chez des patients diabétiques de type 2 obèses atteints du VIH sous antirétroviraux en alternative à l’insulinothérapie n’est pas documentée ; nous rapportons le cas d’un homme de 47 ans séropositif traité dès l’arrêt de l’insuline par l’exenatide. Durant la première année de traitement, l’exenatide, combinée à la metformine et la repaglinide, a permis une perte de poids de 14 kg ; la masse grasse et le tour de taille ont été réduits respectivement de 31 à 25,5 % et de 114 à 103 cm ; le homeostatic model assessment (HOMA) a permis de calculer respectivement la sécrétion β-cellulaire qui est passé de 50 à 78 % ainsi que la sensibilité à l’insuline passant de 28 à 51 % traduisant une diminution du taux de l’hémoglobine glyquée (HbA1c) de 1,9 %. L’exenatide pourrait être une nouvelle option thérapeutique pour les diabétiques de type 2 infectés par le VIH sous antirétroviraux.

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**Mots clés :** Incretinomimétique ; VIH ; Antirétroviraux ; Diabète ; Efficacité

**Abstract**

The use of retroviral drugs in the treatment of infection by human immunodeficiency virus (HIV) is associated, especially for first generations, with side effects such as lipodystrophy, fatty liver and insulin resistance, which may trigger secondary diabetes or worsen existing diabetes. The use of Glucagon-Like Peptide-1 in obese patients with type 2 diabetes on HIV retroviral as an alternative to insulin therapy is not documented; we report the case of a 47-year-old treated with exenatide when insulin was discontinued. During the first year of treatment, exenatide, in combination with metformin and repaglinide, led to a weight loss of 14 kg and fat mass and waist circumference were respectively reduced from 31 to 25.5% and from 114 to 103 cm. Homeostatic model assessment (HOMA) was used to calculate β-cell secretion which increased from 50 to 78% and insulin sensitivity which increased from 28 to 51%, reflecting a decrease in HbA1c by 1.9%. Exenatide may be a new therapeutic option for HIV-infected type 2 diabetes patients undergoing retroviral therapy.

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**Keywords:** Incretin mimetic drug; HIV; Antiretroviral therapy; Diabetes; Efficacy

**1. Introduction**

Exenatide is an incretin mimetic drug used to lower blood glucose in patients with type 2 diabetes mellitus, in association with sulfonylurea and metformin. This new therapeutic class...
decreases fasting and postprandial glycemia by improving postprandial insulin secretion, delaying gastric emptying, reducing glucagon secretion and promoting weight loss [1]. Highly-active antiretroviral therapy (HAART) is now the standard of care for HIV patients. HAART is associated, mainly when protease inhibitors are used, with unwanted cardiometabolic side effects, such as lipodystrophy with central fat accretion, insulin resistance and impaired glucose homeostasis (including diabetes) and dyslipidemia [2]. The toxicity of HAART, particularly of thymidine analogues on adipocytes, is a major determinant of insulin resistance, leading to the pathophysiology of diabetes following antiretroviral treatment. In some cases HAART is also associated with impaired adipocyte differentiation by altering transcription factors including Sterol Regulatory Element Binding Protein–1 and Peroxisome proliferator-activated receptor [3], oxidative stress, production of proinflammatory cytokines [4,5] and cellular aging [5,6].

This case report, hitherto not documented, describes the use of exenatide in an HIV-infected patient with HAART-related diabetes and discusses the potential benefit of such a therapy.

2. History and examination

A 47-year-old male first attended our clinic in 2008. The medical history identified type 2 diabetes in 2001 which was treated with repaglinide. His father also had type 2 diabetes.

Our patient had a documented HIV infection treated since 2006 by a triple drug HAART combining efavirenz (a fixed-dose combination of tenofovir disoproxil fumarate plus emtricitabine) with a good and sustained immunovirological response. Routine lipid profiling showed low HDL-C and high triglycerides together with elevated cholesterol, and the diabetic patient was prescribed statin for primary cardiovascular prevention [2].

From 2006 onwards, bedtime insulin was added (glargine 30 unit/24 h). Weight gain amounted to 23 kg since inception of exogenous insulin. Due to HbA1c being off target (7.1%) in July 2008, despite exogenous insulin, metformin was added (500 mg/24 h per day, increasing to 1000 mg/24 h) as the drug was well tolerated, yet without beneficial changes in anthropometric or biological parameters after three months. At this stage, the patient discontinued insulin due to excess weight gain.

His decision, combined with unsatisfactory glucose control, persuaded us to introduce exenatide therapy as a weight-neutral alternative to insulin [7].

3. Investigation

The following table shows the evolution of various bioanthropometric variables, including body composition. Body fat percentage was measured based on electrical resistance and personal data such as height, weight, age and gender. The measured results closely correlated with the “underwater weighing method” and the Dual Energy X-ray Absorptiometry (DEXA) method, which are said to be the standard measurements methods for measuring body fat percentage, and HOMA-modelling of β-cell function and insulin sensitivity (by HOMA Calculator© the University of Oxford) (Table 1).

During the first year of treatment with exenatide, the patient did not experience hypoglycaemia, and oral antidiabetic drugs dosages were therefore not modified. Regular checks for blood lactic acid level were negative [8]. As regards to HIV infection, immunovirological monitoring was deemed optimal and unaffected by the antidiabetic therapy, indeed the standard level of CD4 count remained between 800 and 1500/mm³. The therapeutic goal was to block retrorviral replication (HIV RNA < 50 copies/mL) and ideally to exceed the threshold of 500 CD4/mm³ [9].

In this case, the weight loss due to exenatide was especially evident in the abdominal region, as shown by the ancillary measure of central adiposity represented by waist circumference. This weight reduction, presumed to be mostly loss of fat, does not suggest wasting secondary to an altered immunovirological status of the patient and is distinct from the wasting syndrome with weight loss including loss of muscle mass. In parallel with weight reduction and loss of central adiposity, treatment with

<table>
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<th>Characteristics</th>
<th>2006</th>
<th>July 08</th>
<th>Oct 08</th>
<th>Nov 08</th>
<th>Mar 09</th>
<th>May 09</th>
<th>Sept 09</th>
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<td>104</td>
<td>101</td>
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<td>BMI (Kg/m²)</td>
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<td>32.6</td>
<td>32.3</td>
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<td>Body fat (%)</td>
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<td>29</td>
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<td>515</td>
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<td>Waist circumference (cm)</td>
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<td>111</td>
<td>105</td>
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<td>HbA1c (%)</td>
<td>7.1</td>
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<td>7.7</td>
<td>7.9</td>
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<td>C-peptide (ng/mL)</td>
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<td>50</td>
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<td>HOMA - S (%)</td>
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<td>51</td>
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</table>

BMI: body mass index; HOMA: homeostatic model assessment; S: insulin sensitivity; β: β-cell function; βxS: HOMA hyperbolic product.

* A body fat percentage was measured based on electrical resistance.
exenatide resulted in satisfactory glycemic control and improved indices of insulin sensitivity and insulin secretion at baseline calculated by HOMA.

To our knowledge, this is the first description of the beneficial use of exenatide on metabolic parameters in an HIV-infected patient with type 2 diabetes. Exenatide led to a sustained decrease in HbA1c, down to target values, a substantial decrease in excess weight and improved quality of life when compared with exogenous insulin administration as shown by Buysschaert et al. [1] and Heine et al. [7].

The antidiabetic treatment was well tolerated up to one-year follow-up, and the diabetes was considered to be under control. This was paralleled by a late beneficial drift in all HOMA indices, in particular the hyperbolic product BxS [10], which represents the underlying insulin secretory capacity adjusted for an individual’s insulin sensitivity.

4. Conclusion

Currently, metformin and to a lesser extent pioglitazone may be considered the choice alternative antidiabetic therapies with the potential to improve certain aspects of glucose disorders in HIV-infected patients [11], especially in those treated with HAART including protease inhibitors, which was not the case with our patient. However, our results show that exenatide may be indicated for the treatment of type 2 diabetes in patients who are HIV positive. This single-case observation suggests a rationale for prospective studies to establish the long-term efficacy and safety of incretinomimetics in treating HIV-related abnormalities in glucose homeostasis.

Acknowledgments

We thank the Infectious Disease Department of Tourcoing Hospital, Northern AIDS Reference Center, Lille University, France.

This case report will be discussed at the Société francophone du diabète (SFD) meeting in Geneva, in March 2011.

References