Incretin mimetics as a novel therapeutic option for hepatic steatosis

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Abstract: Background: Fat accumulation in the liver or non-alcoholic fatty liver disease (NAFLD) is regarded as a key pathogenic factor and component of the metabolic syndrome. It was reported that administration of the incretin mimetic exenatide reversed hepatic steatosis in an obese mouse model. We had the opportunity to study the effect of additional exenatide administration on liver fat content in a patient with type 2 diabetes. Case report: A 59-year-old male with poorly controlled type 2 diabetes was treated with exenatide in addition to metformin monotherapy. Following 44 weeks of exenatide therapy, mean the liver fat measured by liver spectroscopy declined from 15.8% to 4.3%. This dramatic decrease in liver fat was accompanied by significant beneficial changes in several cardiovascular disease risk factors and improvement of all liver enzymes, in particular alanine aminotransferase, the most important marker of liver steatosis. Conclusion: This case report suggests that the incretin mimic exenatide decreases hepatic fat accumulation and may play a role in the future treatment of NAFLD, and the associated insulin resistance and cardiovascular risk factors in an ever-growing high-risk population.

The metabolic syndrome, a cluster of cardiovascular disease factors, is present in the majority of obese type 2 diabetic patients (1). Currently, fat accumulation in the liver or non-alcoholic fatty liver disease (NAFLD) is regarded as a key pathogenic factor and component of this syndrome (2). Therapies aimed at reducing liver fat have been shown to concomitantly improve the risk profile in this high-risk population. For example, both lifestyle interventions resulting in weight loss and administration of thiazolidinediones, which is associated with weight gain, have been associated with decreased liver fat and improvement of (hepatic) insulin sensitivity (3, 4). Furthermore, these studies suggested that the presence of risk factors for cardiovascular disease, in particular low HDL cholesterol and high triglycerides, is strongly related to the amount of liver fat.

Glucagon-like peptide 1 (GLP-1) is an incretin hormone that is secreted by the L cells of the intestine upon meal ingestion. In type 2 diabetic patients, GLP-1 lowers blood glucose levels in a glucose-dependent manner, by potentiating meal-induced insulin production and secretion by the pancreatic β cells, by slowing gastric emptying and by inhibiting glucagon secretion. Also, GLP-1 induces weight loss, possibly because of central inhibition of appetite, and may also improve insulin sensitivity (5). However, GLP-1 has a very short half-life as it is degraded by the ubiquitous enzyme dipeptidyl-peptidase IV (DPPIV). The long-acting, DPPIV-resistant GLP-1 receptor agonist or incretin mimetic exendin-4 (exenatide, synthetic exendin-4) is a 39 amino-acid peptide that binds with high affinity to the GLP receptor. Recently, exenatide was introduced, to the market in the United States as a blood-glucose-lowering-agent. The full scope of the effects of incretin mimetics still needs to be elucidated and the almost ubiquitous presence of the GLP-1 receptor in the human body implies many potential actions. Recently, it was reported that exenatide administration in an obese mouse model reversed hepatic steatosis. This effect was attributed to increased fatty acid oxidation and/or inhibition of de novo lipogenesis (6). At present, it is not clear whether incretin mimetics also affect liver fat content in obese type 2 diabetes patients.
A 59-year-old Caucasian male with type 2 diabetes, treated with metformin, was prescribed exenatide 20μg twice daily, because of poor control (HbA1c: 8.7%; reference values: 4–6%). He was a retired craftsman and had no history of alcohol abuse or viral hepatitis. At baseline, his body weight was 88.5 kg (BMI 28.7 kg/m²), his waist circumference was 98.5 cm and his blood pressure was 157/87 mmHg. The fasting laboratory values were as follows: plasma glucose 14.5 mmol/l, total cholesterol 4.82 mmol/l, HDL cholesterol 1.04 mmol/l, LDL cholesterol 3.29 mmol/l, triglycerides 1.46 mmol/l, alanine aminotransferase (ALT) 46 IU/l, aspartate aminotransferase (AST) 18 IU/l, γ-glutamyltranspeptidase (GGT) 28 IU/l (reference values: 6–48; 10–45; 7–51 IU/l, respectively) and insulin resistance estimated by homeostasis assessment model (HOMA-IR) of 6.36.

Following 44 weeks of exenatide therapy, HbA1c decreased to 8.4% and fasting plasma glucose to 9.9 mmol/l. His body weight fell by 4.7%, from 88.5 to 84.3 kg, and his waist circumference by 2.5 cm.

Liver fat accumulation was quantified in the fasting state using proton magnetic resonance spectroscopy (1H-MRS), a method that has been shown to correlate excellently with liver fat as measured in biopsy samples (7). At three positions (right anterior, right posterior and medial or left anterior), a 15 cm³ spectroscopic volume of interest was positioned, avoiding major blood vessels, intra-hepatic bile ducts and the lateral margin of the liver. Areas of resonances from protons of water and methyl and methylene groups in fatty acid chains of the hepatic triglycerides were evaluated with LCModel (8). Surprisingly, the mean liver fat (average of the three volumes of interest) declined from 15.8% before to 4.3%, i.e. by 73%, after 44 weeks of exenatide therapy (Fig. 1). This dramatic decrease in liver fat was accompanied by significant beneficial changes in several cardiovascular disease risk factors: blood pressure decreased to 140/85 mmHg, fasting LDL cholesterol to 2.67 mmol/l, triglycerides to 0.69 mmol/l, HOMA-IR to 2.51, while HDL cholesterol increased to 1.27 mmol/l. In accordance with the MRS findings, all liver enzymes, and in particular ALT, the most important marker of liver steatosis (9), improved. This value decreased from 46 to 20 IU/l, while AST decreased from 18 to 13 IU/l, and GGT from 28 to 23 IU/l.

Discussion
Experimental evidence indicates that exenatide, by activating the GLP-1 receptors, effectively

![Fig. 1. Abdomen magnetic resonance imaging scans indicating volume of interest in the anterior left hepatic lobe from which proton magnetic resonance spectra (CH₂ peak at 1.3 p.p.m. is the main signal of lipids) were obtained before (A) and after (B) exenatide treatment.](image-url)
Exenatide and hepatic steatosis

In recent years, incretin mimetics have demonstrated their ability to influence beneficially a variety of abnormalities in type 2 diabetes, including defective insulin secretion, hyperglucagonaemia as well as excessive body weight and appetite (5). Now it seems that incretin mimetics also have salient effects on NAFLD and the associated cardiovascular risk factors. Future long-term intervention studies are required to confirm these findings.

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