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ORIGINAL ARTICLE

Effect of incretin therapies compared to pioglitazone and gliclazide in non-alcoholic fatty liver disease in diabetic patients not controlled on metformin alone: An observational, pilot study☆

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KEYWORDS
Non-alcoholic fatty liver disease;
GLP-1;
Thiazolidinediones

Abstract
Aim: To compare the effect of different hypoglycemic drugs on laboratory and ultrasonographic markers of non-alcoholic fatty liver disease (NAFLD) in patients with type 2 diabetes not controlled on metformin alone.
Methods: Prospective study of diabetic patients treated with metformin in combination with gliclazide, pioglitazone, sitagliptin, exenatide, or liraglutide. NAFLD was assessed by abdominal ultrasound and NAFLD fibrosis score was calculated at baseline and 6 months.
Results: Fifty-eight patients completed 6 months of follow-up: 15 received gliclazide, 13 pioglitazone, 15 sitagliptin, 7 exenatide, and 8 liraglutide. NAFLD affected 57.8% of patients at baseline, and its ultrasonographic course varied depending on changes in weight ($P = .009$) and waist circumference ($P = .012$). The proportions of patients who experienced ultrasonographic improvement in the different treatment groups were: 33.3% with gliclazide, 37.5% with pioglitazone, 45.5% with sitagliptin, 80% with exenatide, and 33% with liraglutide ($P = .28$).

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Conclusions: Qualitative ultrasonographic NAFLD improvement in diabetic patients treated with metformin in combination with other hypoglycemic drugs is associated to change over time in weight and waist circumference. Long-term clinical trials are needed to assess whether incretin therapies result in better liver outcomes than other hypoglycemic therapies.

PALABRAS CLAVE
Esteatosis hepática no alcohólica;
Glucagon-like peptide-1;
Tiazolidindionas

Efecto de las terapias incretínicas comparadas con pioglitazona y gliclazida en la esteatosis hepática no alcohólica de los pacientes diabéticos no controlados solo con metformina: estudio observacional piloto

Resumen
Objetivo: Comparar el efecto de diferentes hipoglucemiantes en indicadores analíticos y ecográficos de la esteatosis hepática no alcohólica (EHNA) en pacientes con diabetes tipo 2 no controlados solo con metformina.
Métodos: Estudio prospectivo de pacientes diabéticos tratados con metformina, en combinación con gliclazida, pioglitazona, sitagliptina, exenatida o liraglutida. En el momento basal y a los 6 meses la EHNA fue valorada por ecografía abdominal y se calculó el índice de fibrosis de la EHNA.
Resultados: Cincuenta y ocho pacientes completaron los 6 meses de seguimiento: 15 recibieron gliclazida, 13 pioglitazona, 15 sitagliptina, 7 exenatida y 8 liraglutida. La EHNA afectó basalmente al 57,8% de los casos y su evolución ecográfica varió dependiendo de la evolución del peso ($P = 0{,}009$) y de la cintura ($P = 0{,}012$). Los porcentajes de sujetos que experimentaron una mejoría ecográfica en los diferentes grupos de tratamiento fueron: 33,3% con gliclazida, 37,5% con pioglitazona, 45,5% con sitagliptina, 80% con exenatida y 33% con liraglutida ($P = 0{,}28$).
Conclusiones: La evolución ecográfica cualitativa de la EHNA en el paciente diabético tratado con metformina en combinación con otros hipoglucemiantes está vinculada a la evolución del peso y del perímetro de cintura. Son precisos ensayos clínicos de larga duración para evaluar si las terapias incretínicas se asocian a mejores resultados hepáticos que otras terapias hipoglucemiantes.

Introduction

Non-alcoholic fatty liver disease (NAFLD) affects 69.4% of diabetic patients[1] and is associated with increased mortality from both cardiovascular and hepatic causes.[2] NAFLD is defined as the accumulation in the liver of fat representing more than 5–10% of liver weight[3] and progresses in 12–20% of patients to steatohepatitis with mild to moderate fibrosis. In 13% of patients, fibrosis evolves to cirrhosis in 4–5 years.[4] It is expected that in 2020, in parallel to the worldwide epidemic of obesity. NAFLD will become the leading cause of liver transplantation.[5]

The most widely used treatment for NAFLD consists of a low-calorie diet and physical exercise, with the aim of reducing weight by 5–10% in 6–12 months.[6] Because of the difficulty of the long-term maintenance of these dietary measures, the efficacy of different drugs in NAFLD is being tested.[3] To date, most studies have been conducted with metformin and pioglitazone. Metformin has not shown beneficial effects on liver histology,[7] and the American Association for the Study of Liver Disease has advised against its use.[6] As regards pioglitazone, the results of some trials could warrant its administration in NAFLD, but long-term safety problems have been reported.[8] Data regarding the role of dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists are still limited.[9]

Metformin has been shown to decrease overall mortality in diabetic patients,[10] and multiple clinical guidelines consider it the drug of first choice in these patients. In clinical practice, 53.9% of diabetic patients on metformin alone are not controlled ($HbA_{1c} > 7\%$).[11] To select a second hypoglycemic agent added to metformin in these uncontrolled patients, treatment could be individualized based on age, diabetes duration, associated complications, or the risk of hypoglycemia.[12] The hypothesis that the effect of second-line hypoglycemics in NAFLD could also be a criterion for the individualization of treatment in diabetic patients not controlled on metformin alone has yet to be proven.

The objective of this study was to compare the effect of different second-step hypoglycemic drugs on qualitative laboratory and ultrasonographic markers of NAFLD in patients with type 2 diabetes mellitus not controlled on metformin alone.