



Insulin treatment of people with diabetes mellitus and chronic liver disease

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DEAR EDITOR,

We agree with the overall content of the article published by Diego García-Compeán, *et al.* in volume 14 of 2015¹ concerning the treatment of diabetes mellitus (DM) in patients with liver cirrhosis (CLD). Therein the authors emphasize the difficulties encountered in clinical practice, including especially the high hypoglycemic risk associated with insulin, and suggest the use of rapid acting analogues and insulin degludec to minimize it.

For many years our group has dealt with similar problems and has accrued some experience with insulin utilization in CLD: this further strengthens what is stated in the above-mentioned article. Insulin treatment is frequently required in patients with DM and CLD at doses which, however, may vary significantly. For example, insulin requirement may be decreased in patients with decompensated CLD due to impaired gluconeogenesis and hepatic insulin breakdown. However, there is evidence that the association of CLD with type 2 diabetes (T2DM) is characterized by variable degrees of insulin resistance.²⁻⁴ In that case, larger doses of exogenous insulin are required, potentially leading to unsatisfactory glucose metabolism and increased hypoglycemic risk. Thus, careful glucose monitoring and frequent treatment adjustments may be necessary. Moreover, in patients requiring high-carbohydrate diets expected to cause postprandial hyperglycemia (e.g. those with hepatic encephalopathy), rapid-acting insulin analogs such as lispro, aspart, or glulisine may be particularly useful.⁵

Nevertheless, a guideline is not currently available defining which insulin preparation may be considered of choice in patients with CLD and T2DM. In addition, regular

human insulin and rapid analog preparations are commercially available for both home and hospital use. As a result, many CLD patients are often light-heartedly switched from one preparation to the other during the course of their disease.

Our recent data on the comparison between insulin lispro and regular insulin administered to two groups of 50 subjects matched for anthropometric and clinical parameters support the suggestion made by Diego García-Compeán, *et al.* All gave their informed consent to the study, which was conducted according to the Declaration of Helsinki and approved by the local Ethical Committee. Both groups were suffering from diet-unresponsive T2DM and Child-Pugh A or B stage CLD and received 12 weeks of comparable doses of insulin lispro or regular insulin before the three main meals plus bedtime glargine to ensure fasting glucose levels of 90 to 110 mg/dL.

Mean glucose levels observed immediately before the three meals were similar in the lispro group and in the regular insulin group. Glucose excursions at 1 and 2 h were comparable with each other in patients on lispro but higher at 1 h as compared to 2 h (158 ± 25 mg/dL *vs.* 118 ± 20 mg/dL, respectively, $p < 0.05$) in those treated with regular insulin, whose glucose excursions were higher than in their lispro-treated counterparts both at 1 h (155 ± 29 mg/dL *vs.* 53.7 ± 16.5 mg/dL, respectively, $p < 0.01$) and at 2 h (118 ± 20 mg/dL *vs.* 30 ± 14.3 mg/dL, respectively, $p < 0.01$). Moreover, patients on regular insulin showed significantly lower glucose levels in the late post-meal status (3-4 h) and during the night (from 01.00 to 03.00 a.m.) - due to the additive effect of regular and glargine insulin - despite the total insulin dose remaining statistically undistinguishable between the two groups (51 ± 6 for regular

insulin *vs.* 50 ± 4 IU/day for lispro). Also, the number of hypoglycemic episodes recorded in the final two weeks was significantly higher with regular insulin than with lispro (9.7 ± 3.7 *vs.* 1.8 ± 1.0 respectively; $p < 0.001$). Finally, overall glucose tolerance was better with lispro: a significantly lower glucose Δ AUC (124 ± 44 *vs.* 315 ± 58 ng·h/mL, respectively, $p < 0.05$) was associated with a marker of lower endogenous post-prandial insulin secretion (C-peptide Δ AUC 18.9 ± 7.8 *vs.* 35.5 ± 8.9 ng h/mL, respectively; $p < 0.05$).

Our data suggest that in compensated CLD patients with diet-unresponsive T2DM, lispro provides more effective and early hepatic insulinization than regular insulin and this might decrease liver glucose output more easily. This leads to better glucose control than observed with regular insulin. Furthermore, lispro grants a lower nighttime hypoglycemic risk than regular insulin. Based on this, we would recommend lispro as the first choice therapeutic option in compensated cirrhotic patients with type 2 DM.

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