

Insulin-Like Growth Factor-I, Liver Function, and Hypogonadism in Rats With Experimentally Induced Cirrhosis

To the Editor:

We acknowledge the editorial by Dr. Mezey¹ devoted to our article in the March 2000 issue of HEPATOLOGY regarding the beneficial effects of insulin-like growth factor-I (IGF-I) on testicular atrophy in rats with advanced cirrhosis.² However some statements of the editorialist deserve clarification. Dr. Mezey rules out any influence of an improvement of liver function on the effects of IGF-I on testicular atrophy. He mentions that no improvement in liver function tests was observed in cirrhotic rats after IGF-I administration and that this lack of beneficial effect on liver function is in disagreement with our previous findings showing a hepatoprotective effect of IGF-I in cirrhotic rats.³ This statement is surprising because in the article published in the March issue of HEPATOLOGY we have included values of liver function tests *before* IGF-I treatment (to show that the two groups of treated and untreated cirrhotic rats were comparable *before* initiation of therapy) but no specific values of liver function parameters *after* IGF-I treatment were given. In fact, in the report we mentioned that we observed an inverse correlation between albumin and the histopathologic score of testicular damage *after* IGF-I treatment, indicating that serum albumin increased in those rats showing recovery of normal testicular structure (which were the ones treated with IGF-I). Data not given in this report show that these rats show not only an increase in serum albumin (from 353 ± 27 to 440 ± 15 mmol/L, $P < .05$) but also a decrease in bilirubin (from 16.7 ± 5.0 to 6.7 ± 1.7 mmol/L, $P < .05$). Therefore, there is no disagreement between data presented in our report in the March issue of HEPATOLOGY and our previous reports. Nevertheless, as it is stated in the Discussion of the report, this improvement of liver function is moderate and cannot be fully responsible for the dramatic amelioration of testicular histopathology, an effect that is likely related to the direct effect of IGF-I on the testis.

The editorial also refers to published data showing that IGF-I stimulates proliferation of human cultured hepatic stellate cells and increases α_1 (I) collagen message and type I collagen accumulation, thus suggesting that IGF-I may have profibrogenic properties.⁴ These *in vitro* studies are in apparent contradiction with our previous results showing an amelioration of the fibrosis score in cirrhotic rats after IGF-I treatment.³ We have calculated the fibrosis score (maximum: 20 points) after IGF-I therapy in the livers from the rats used in our report. Again, rats receiving IGF-I showed a fibrosis score significantly lower (14.6 ± 0.3 points) than that observed in untreated cirrhotic rats (17.0 ± 0.5 points, $P < .05$), indicating an *in vivo* antifibrogenic activity of IGF-I. This effect may be because of the ability of IGF-I to reduce oxidative stress in hepatocytes and to protect mitochondrial function in these cells.³

On the other hand, although in the editorial it is mentioned that an increase in IGF-I binding protein 3 (IGFBP3) might occur in cirrhotic patients and this might contribute to a reduction in the tissue bioavailability of the hormone (by sequestration of IGF-I in circulation), the common situation in cirrhosis is that of a marked fall in IGFBP3.^{5,6} Although an increase in IGFBP3 was found in rats with early experimental cirrhosis,⁷ decompensated cirrhosis is associated with low IGFBP3 values. However in these cases low IGFBP3 might not be able to compensate the deleterious effects of IGF-I deficiency.

INMA CASTILLA-CORTAZAR, M.D.
Department of Human Physiology
School of Medicine
University of Málaga
Málaga, Spain

JORGE QUIROGA, M.D.
JESUS PRIETO, M.D.
Liver Unit and Department of Internal Medicine
University Clinic of Navarra
University of Navarra
Pamplona, Spain

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REFERENCES

1. Mezey E. Insulin-like growth factor I and hypogonadism in cirrhosis. HEPATOLOGY 2000;31:783-784.
2. Castilla-Cortázar I, García M, Quiroga J, Díez N, Díez-Caballero F, Calvo A, Díaz M, et al. Insulin-like growth factor-I reverts testicular atrophy in rats with advanced cirrhosis. HEPATOLOGY 2000;31:592-600.
3. Castilla-Cortázar I, García M, Muguerza B, Quiroga J, Pérez R, Santidrián S, Prieto J. Hepatoprotective effects of insulin-like growth factor-I in rats with carbon tetrachloride-induced cirrhosis. Gastroenterology 1997;113:1682-1691.
4. Svegliati-Baroni G, Ridolfi F, Di Sario A. Insulin and insulin-like growth factor-I stimulate proliferation and type I collagen accumulation by human hepatic stellate cells: differential effects on signal transduction pathways. HEPATOLOGY 1999;29:1743-1751.
5. Assy N, Hochberg Z, Amit T, Shen-Orr Z, Enat R, Baruch Y. Growth hormone-stimulated insulin-like growth factor (IGF) I and IGF-binding protein-3 in liver cirrhosis. J Hepatol 1997;27:796-802.
6. Donaghy A, Ross R, Gimson A, Hughes SC, Holly J, Williams R. Growth hormone, insulin-like growth factor-1, and insulin-like growth factor binding proteins 1 and 3 in chronic liver disease. HEPATOLOGY 1995;21:680-688.
7. Picardi A, Costa de Oliveira A, Muguerza B, Tosar A, Castilla-Cortázar I, Quiroga J, Santidrián S, et al. Low doses of insulin-like growth factor-I improve nitrogen retention and food efficiency in rats with early cirrhosis. J Hepatol 1997;26:191-202.

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