Evaluation of the analgesic, osteo- and neuroprotector effects of baricitinib in a murine model of type-1 diabetes

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INTRODUCTION: Type 1 diabetes (T1D) is associated with numerous complications, including loss of nerve fibers innervating bone and a pathological loss of trabecular bone, all of them, negatively affecting the quality of life of patients. There are no therapies that efficaciously reverse bone complications. Recent studies have reported that Janus kinase (JAK) pathway inhibitors exhibit antinociceptive, antiresorptive and neuroprotector properties. In the present study, we simultaneously evaluated the osteo and neuroprotector effect of baricitinib (JAK1 and JAK2 inhibitor) in a mouse model of T1D.

METHODS: Female ICR mice were housed in groups of 4, in a temperature and humidity-controlled environment. All experimental procedures were performed following the Mexican Official Norm of Animal Care and Handing (NOM-062-ZOO-1999). Moreover, the protocol was approved by the Institutional ethics committee of the Unidad Académica Multidisciplinaria Reynosa Aztlan of the Universidad Autónoma de Tamaulipas. At 13 weeks of age, animals received five daily administrations of streptozotocin (STZ; i.p, 50 mg/kg) control to induce T1D or citrate as negative control. Eighteen weeks post-first injection of STZ, animals were administered baricitinib (40 mg/kg, twice a daily, p.o. for 28 days) or vehicle. Mechanical sensitivity evaluations were performed, before and each week after the treatment, using the up-down method. Animals were sacrificed by intracardiac perfusion at 35 weeks of age. Subsequently, lower extremities were harvested for microcomputed tomography and immunohistochemistry analysis.

RESULTS SECTION: Mice with T1D had a significant increase in blood glucose levels compared to control group. These also showed mechanical hypersensitivity, loss of trabecular femoral bone and lower density of $CGRP^+$ sensory and TH^+ sympathetic nerve fibers as compared to control mice. The treatment with Baricitinib reduced the mechanical hypersensitive in to T1D mice; however, it did not reverse the trabecular bone loss and sensory and sympathetic denervation at the femoral neck.

DISCUSSION: Our results demonstrate that baricitinib at the doses and period administered has an antinociceptive effect, but not an osteoprotector nor neuroprotector in a mouse T1D model.

SIGNIFICANCE/CLINICAL RELEVANCE:

1. Results support that baricitinib is a potent therapeutic tool antinociceptive in a murine model of type 1 diabetes.
2. Baricitinib does not have an antiresorptive nor neuroprotector in mouse model of type 1 diabetes.

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