Enteral insulin attenuates fatty liver signs and symptoms in mice on a high-fat diet

Rifaat Safadi, 1 Ahmad Salhab, 1 Johnny Amer 2 Daniel J. Weiss, 1 Daniela Blumenfeld, 2 Yoav Mintz, 3 Nikolai Künicher, 3 Miriam Kidron 1
Liver Unit, Hadassah Medical Center, Jerusalem, Israel; 2 Surgical Innovation and Technology Center, Hadassah Medical Center, Jerusalem, Israel; 3 Oramed Pharmaceuticals Inc.

BACKGROUND
Nonalcoholic fatty liver disease (NAFLD) is now the most common liver disorder in the USA, affecting >90% of morbidly obese individuals and often clustering with prediabetes or overt type 2 diabetes mellitus. Approximately 40% of NAFLD patients progress to nonalcoholic steatohepatitis (NASH), the most common cause of cryptogenic cirrhosis, which subsequently can exacerbate to advanced fibrosis. These patients show increased risk of hepatic carcinoma and cardiovascular and liver-associated mortality. While its exact pathogenesis remains unclear, insulin resistance and obesity are considered contributing and risk factors, suggesting effective blood glucose control as a means of preventing and managing NAFLD.

OBJECTIVE
To establish a proof-of-concept for the therapeutic value of oral insulin in attenuating inflammatory processes associated with chronic liver disease.

METHODS
C57Bl/6J mice (n=33) were maintained on a high-fat diet (HFD) for 16 weeks, and were administered daily insulin (5.6 μg/kg), intraperitoneally (IP), or sham saline treatment (n=15) during the last three weeks. At the end of the treatment period, peripheral blood and liver biopsy samples were collected to analyze inflammatory and fibrosis markers and were subjected to histological staining. Serum samples were collected for analysis of aspartate aminotransferase (AST), alanine transaminase (ALT), and glucose levels. Mice were then randomized into three groups: 2-5 mice/group, and were treated daily with insulin (5.6 μg/kg), delivered via a duodenal feeding tube. Histological and biochemical analyses were performed on day 60 and week 16 of treatment.