Baseline interleukin1beta expression in peripheral blood monocytes predicts the extent of weight loss and nonalcoholic fatty liver improvement in obese subjects with prediabetes or type 2 diabetes

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Background: Non-alcoholic fatty liver disease (NAFLD) represents a hallmark of metabolic syndrome. Interleukin-1β (IL-1β), a well-studied cytokine involved in obesity-related systemic inflammation as well as in the pathogenesis of type 2 diabetes (T2D), promotes hepatic steatosis by stimulating triglycerides and cholesterol accumulation in primary liver hepatocytes and lipid droplets formation. The most compelling evidence for a major role for IL-1β in metabolic imbalance and inflammation comes from the recent Canakinumab Anti-inflammatory Thrombosis Outcome (CANTOs)trial, where inhibition of IL-1β pathway was associated with a reduction of cardiovascular events in high-risk patients.

Purpose: The present study was designed to determine: i)whether an equal degree of weight loss by liraglutide or lifestyle changes has a different impact on NAFLD extent and IL-1β expression in peripheral blood mononuclear cells from obese subjects with prediabetes or early T2D; ii)whether baseline IL-1β levels may predict the extent of weight loss and related metabolic changes.

Methods: Thirty-two metformin-treated obese subjects with prediabetes [impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) or both (n=16)] or newly diagnosed T2D (n=16), were randomized to the glucagon-like peptide receptor agonist (GLP-RA) liraglutide (1.8 mg/d) or lifestyle counselling until achieving a modest and comparable weight loss (–7% of initial body weight). Visceral (VAT) and adipose tissue distribution were assessed by magnetic resonance. Gene expression of IL-1β in peripheral blood mononuclear cells was assessed by real time PCR.

Results: At baseline, IL-1β positively correlated to body mass index (BMI) (rho=0.421, p=0.016), fasting plasma glucose (rho=0.415, p=0.018), HbA1c (rho=0.349, p=0.050), VAT (rho=0.388, p=0.028), NAFLD (rho=0.454, p=0.009), platelet count (rho=0.510, p=0.003), chemerin (rho=0.455, p=0.009) and interleukin-1 receptor agonist (IL1-RA) (rho=0.519, p=0.002). After achievement of the weight loss target in the two groups, a comparable reduction of IL-1 β ($p<0.001$ lifestyle changes; p=0.029 liraglutide treatment) was observed in both arms, in parallel with a comparable improvement in glycaemic control, C-reactive protein (CRP),BMI and NAFLD. Furthermore, basal levels of IL-1β correlated directly with delta BMI (p=0.015) and delta NAFLD (p=0.002) (Figure 1).

Conclusion: In obese patients with initial impairment of glucose metabolism, IL-β-driven inflammation correlates with glycaemic control, adipose tissue distribution and platelet count. Successful weight loss, achieved with either lifestyle changes or an incretin-based therapy, is associated with a significant reduction of both IL-1β levels and NAFLD degree. Of interest, basal levels of IL-1β predicts the extent of weight loss and NAFLD improvement, regardless of the intervention. Our results may set the stage for ad-hoc studies investigating the usefulness of baseline IL-1β a levels as a drug-response biomarker.

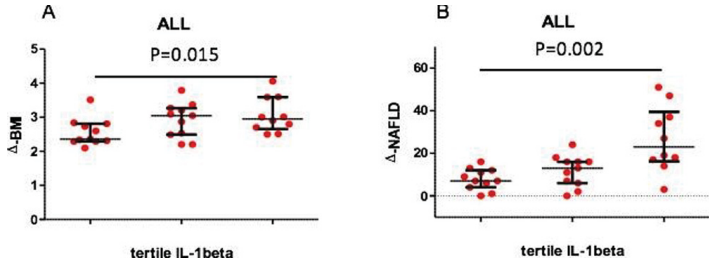

Figure 1