Modulation of mitochondrial dynamism in Kupffer cells impacts systemic metabolism

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Background: Kupffer cells (KCs) are hepatoresident macrophages that are essential for liver physiology and contribute to the development of nonalcoholic hepatic steatosis (NAFLD). The liver of patients with MAFLD shows different expressions of some key regulators of inner mitochondrial membrane fusion compared with healthy subjects, including OPA1 protein, which is a mitochondrial protein whose activity promotes mitochondrial fusion and modulation of oxidative phosphorylation.
Aims: Given the close interaction that KCs have with cells in the hepatic niches, they play both a crucial immune and metabolic role, which is why their mitochondria are critical for their function. This project aims to investigate how modulation of OPA1-driven mitochondrial fusion in KCs can affect lipid metabolism and immune response at the systemic and hepatic levels.
Methods: Mice selectively lacking OPA1 in the KCs were fed a Standard Diet or a High Fat Diet for 20 weeks. The immune phenotype was assessed by cytofluorimetry while the metabolic profile by in vivo indirect calorimetry and with plasma and tissue lipid profile analysis. Single cell RNA sequencing was also performed to profile the impact of OPA1 deficiency on KC function and possible paracrine effects on hepatocytes.
Results: Under standard dietary conditions, mice selectively lacking OPA1 in KCs show a different metabolic substrate preference compared to wild type, with an immunophenotype characterized by a higher proportion of pro-resolution KC2 than pro-inflammatory KC1. Functionally, KCs also exhibit dissimilar phagocytic and proliferative capacity. During the high-fat diet, we observed a significant reduction in liver fibrosis.
Conclusions: Taken together, these data suggest that OPA1 plays a key role in the function of Kupffer cells and that the lack of OPA1, causing metabolic reprogramming, affects their interaction with resident liver cells, influencing the development of fibrosis and the progression of MAFLD.

Efficacy of Oral Semaglutide on Cardiovascular Risk in Patients with Type 2 Diabetes Mellitus: A Real-Life Study

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Background: The efficacy of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in glycemic control and cardiovascular risk reduction in type 2 diabetes mellitus (T2DM) is well established. Real-world, non-interventional studies are increasingly essential to gather information from routine clinical practice.
Objective of the Study: This multicenter, observational, retrospective, single-arm study aims to assess the effect of oral semaglutide on surrogate markers of cardio-metabolic risk (such as Visceral Adiposity Index, triglyceride-glucose index, Lipid Accumulation Product), as well as on glycemic control, renal function markers (creatinine, eGFR, microalbuminuria), and lipid profile, in adult patients with T2DM who are naive to GLP-1 RA therapy.
Materials and Methods: A total of 154 adult diabetic patients (106 male, 48 female; mean age 64.4±10.5 years) with an average disease duration of 10 years (10.1±8.4) were evaluated. Patients initiated oral semaglutide treatment according to AIFA note 100 guidelines and were followed at diabetes outpatient clinics in ASST Bergamo Ovest, Garda, and Mantova. Clinical, biochemical, and anthropometric data for each patient were collected at the beginning of treatment (T0) and after 12 months (T12).
Results: The main results are presented in the table below:

Variables	T0	T12	P-value
BMI, Kg/m² (mean±SD)	31.2±5.2	29.6±5.1	<0.001
Waist circumference, cm (mean±SD)	105.9±10.3	99.9±9.9	<0.001
Fasting glucose, mg/dL (mean±SD)	154.7±43.1	124.8±30.5	<0.001
HbA1c, % (mean±SD)	7.8±1.2	6.7±0.9	<0.001
Total cholesterol, mg/dL (mean±SD)	171.9±40.0	154±34.7	<0.001
HDL cholesterol, mg/dL (mean±SD)	47.7±11.9	52.0±12.2	<0.001
LDL cholesterol, mg/dL (mean±SD)	93.8±36.1	81.5±80.8	0.05
Triglycerides, mg/dL (mean±SD)	157.2±74.2	132.9±57.0	<0.001
eGFR, ml/min/1.73m² (mean±SD)	62.8±17.2	67.7±20.6	<0.001
Urinary albumin/creatinine ratio, mg/g [median (IQR)]	38.5 (14.3-81.8)	12 (5.6-34.3)	<0.001
Systolic blood pressure, mmHg (mean±SD)	134.8±14.6	131.4±15.2	0.015
Diastolic blood pressure, mmHg (mean±SD)	78.3±8.7	75.8±8.5	0.003
Visceral Adiposity Index [median (IQR)]	2.4 (1.6-3.4)	1.7 (1.0-2.6)	<0.001
Triglyceride-glucose index [median (IQR)]	5.9 (4.8-5.2)	4.8 (4.7-4.9)	<0.001
Lipid Accumulation Product [median (IQR)]	77.0 (52.8-111.6)	56.1 (35.2-80.9)	<0.001

Conclusions: Exposure to oral semaglutide for 12 months in T2DM patients resulted in significant improvements in glycemic control, renal function parameters, and surrogate markers of cardiovascular risk.