# Oral Lipid Challenge: The Effects of Saturated Fat on Hepatic Gluconeogenesis, ATP Production, and Fat Accumulation in Healthy Humans

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## Introduction:

Reduced muscle glucose uptake and increased hepatic gluconeogenesis are early features of insulin resistance in humans. The oral ingestion of a single bolus of saturated fatty acids (FA) has been shown to rapidly induce insulin resistance [1], while short-term lipid infusion of unsaturated FA has also shown to lead to increased gluconeogenesis due to greater lipid availability [2]. Since overnutrition in humans is generally associated with increased intake of saturated FA, this study aimed to use non-invasive MRS measurements to examine the short-term effects of an oral load ingestion of saturated FA on net hepatic gluconeogenesis (GNG), hepatic ATP production, and hepatic fat content (HCL); while assessing changes in endogenous glucose production (EGP), rates of lipid oxidation, and whole body insulin sensitivity.

**Fig 1.**

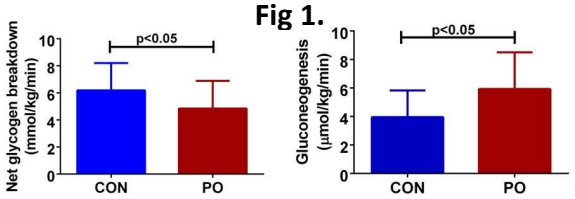
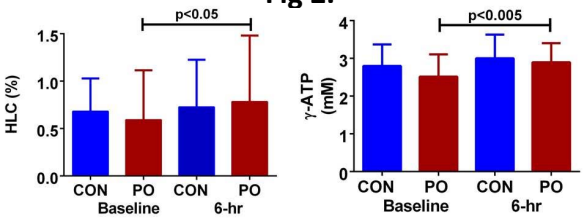



**Fig 2.**




## Subjects and Study Protocol:

Healthy male volunteers (n=14, Age 25.6±5.3 yr, BMI of 22.5±1.1 kg/m$^2$) (mean±SD) maintained a diet of 60% carbohydrates, 25% fat, 15% protein for three days prior to the study. On the night before, a 800-kcal meal was consumed before a 22 hr fast. Baseline (HCL, liver ATP, liver glycogen) measurements began at 6:30 a.m. the next morning before ingestion of 1.2±0.1 g/(kg body weight) palm oil (PO), or placebo (control, CON) at 8:00 a.m. The effects of PO or CON on liver fat and liver ATP were assessed from baseline and 6-hr measurements; and rates of net glycogen breakdown from linear regression analysis of liver glycogen measurements conducted at baseline, 3-hr, and 6-hr. EGP was determined from continuous [$^2H_2$] glucose administration beginning at 5:00 a.m., and changes in lipid oxidation rates were assessed from indirect calorimetry measurements (baseline, and 6-hr). Whole body insulin sensitivity was determined from a 2-hr hyperinsulinemic-euglycemic clamp which began at 2:00 p.m.

## Materials and Methods or MRS measurements:

All measurements were conducted on a whole body 3.0 T Achieva MRI (Philips Healthcare, The Netherlands). $^1$H-MRS Liver fat was assessed with a single voxel (30x30x20 mm$^3$) STEAM sequence (TR/TE: 5000/10ms, NSA: 16) to assess water content, and a (VAPOR) water-suppressed STEAM sequences (TR/TE: 3000/10ms, NSA: 16) to assess fat content [3]. $^{31}$P-MRS proton decoupled liver ATP measurements were conducted with a 3D ISIS localized sequence (Voxel: 60 x 60 x 60 mm$^3$, TR: 6000ms, NSA:128, WALTZ-4, T=13 min), and a 14 cm $^{31}$P surface coil (Philips Healthcare, The Netherlands). Absolute concentrations of γ-ATP were determined as shown previously [4]. Finally, $^{13}$C-MRS pulse acquire proton decoupled liver glycogen measurements (TR: 230 ms, NSA: 2x4000, CW, T=30 min) were conducted with a 7 cm $^{13}$C/$^1$H coil (PulseTeq, UK), with the quantification of rates of hepatic glycogen breakdown shown previously [5].

## Results:

Oral lipid intervention resulted in a 30% increase of plasma free FA (mean±SD) (PO: 557±188 vs. CON: 387±173 µmol/l, p<0.05) (paired t-test), and a 25% decrease of whole body insulin sensitivity (PO: 5.39±1.92 vs. CON: 7.20±2.84 mg/kg/min, p<0.001). There was no difference in EGP production between interventions (PO 1.9±0.2 µmol/kg/min vs. CON 1.8±0.3 µmol/kg/min). However, the increase in saturated FA reduced rates of net glycogen breakdown by 21% (PO: 5.12±2.08 vs. CON 6.50±2.00 µmol/kg/min, p<0.05), and led to increased rates of GNG (PO: 5.65±2.08 vs. CON 3.53±1.62 µmol/kg/min, p<0.05) (Fig 1). Rates of lipid oxidation increased at during PO intervention (Baseline: 0.86±0.36 vs 6-hr: 1.24±0.41 mg/kg*min, p<0.001), but remained constant during CON (Baseline: 0.83±0.34 vs 6-hr: 0.93±0.45 mg/kg*min, p>0.2). Additionally, increased lipid oxidation during PO intervention corresponded with a 32% increase in HCL (Baseline: 0.59±0.54% vs. 6-hr: 0.78±0.70%, p<0.05), and 15% increase in liver γ-ATP concentrations (Baseline: 2.52±0.59 mM vs. 6-hr: 2.89±0.51 mM, p<0.005) (Fig 2).

## Discussion:

Oral ingestion palm oil increased the availability of saturated FA, decreased whole body insulin sensitivity, and stimulated gluconeogenic flux in the liver. The increase in GNG was accompanied with an increase in FA oxidation, liver fat accumulation, and ATP production. This provides evidence that a single oral bolus of saturated fat leads to a decreased whole body insulin resistance, and increased gluconeogenesis through free FA oxidation and ATP production in healthy subjects.

## References:

1. Nowotny B et al, Diabetes (2013). 2. Krssak M et al, Diabetes (2004). 3. Begovatz P et al, ISMRM abstract #(2419).
4. Laufs A et al, MRM (2013). 5. Begovatz P et al, ISMRM abstract #1963 (2013).