Conférence

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Resveratrol in the management of obesity-related fatty liver disease: a randomized, double-blind, placebo-controlled clinical trial

A l’invitation du Pr Bart Staels
UMR 1011 «Récepteurs nucléaires, maladies cardiovasculaires et athérosclérose»
Summary

Non-alcoholic fatty liver disease (NAFLD) features hepatocyte triglycerides accumulation (steatosis) associated with abdominal obesity, insulin resistance (IR), increased cardiovascular risk, and may progress to cirrhosis and end-stage liver disease. Weight-loss is effective treatment, but a well-recognized clinical challenge. Potential pharmacological treatment will ideally target both hepatic and cardiometabolic dysregulation. Resveratrol has shown promising results in animal models of obesity/NAFLD, preventing the development of steatosis, IR, inflammation and dyslipidemia.

**Aim**: To investigate the efficacy of nutraceutical trans-resveratrol (t-resv) on hepatic and cardiometabolic dysregulation of NAFLD in humans.

**Methods**: 20 overweight/obese men with NAFLD, randomized to either 3000mg t-resv (1500mg b.d.) or placebo daily for 8 weeks.

**Primary outcome**: Peripheral IR, (euglycemic-hyperinsulinemic clamp)

**Secondary outcomes**: Hepatic triglycerides content (HepTrig) and abdominal adipose tissue topography: subcutaneous (SAT) and visceral (VAT), (magnetic resonance spectroscopy and imaging); plasma adiponectin: total (TA) and high molecular-weight (HMW), oxidative-stress: isoprostanes, TAC, GPX, FRAP, SOD; inflammatory and liver biochemistry; fasting respiratory quotient (RQ) and resting metabolic rate (RMR), (indirect calorimetry); plasma t-resv concentration (UPLC-MS).

**Results**: Dosage (3000mg= 43.2±1mg/kg/lean body weight) was well tolerated. Peak plasma concentration for t-resv was 65.7±35.9ng/mL. The area under the concentration versus time curve (AUC$_{0-24}$) was 704.8±254.4ng/mL/hr. At baseline, patients presented with profound IR: glucose disposal rate (GDR)= 2.7±0.4mg/kg/min; HepTrig ranged from 6 to 54%. T-resv treatment did not result in change in GDR(p=0.3), HepTrig(p=0.4), RQ(p=0.2), RMR(p=0.7), SAT(p=0.6), VAT(p=0.5), isoprostanes (p=0.4), TAS(p=0.4), GPX(p=0.2), FRAP(p=0.6), SOD(p=0.2) or TA(p=0.4), but the HMW:TA ratio decreased significantly (0.4±0.2 to 0.3±0.1µg/mL, p=0.02). T-resv treatment was associated with significant raise in aminotransferases (ALT: 57±24 to 73±34U/L, p=0.02, AST: 36±9 to 45±15U/L, p=0.03), IL-10 (6.0±5.6 to 7.2±5.0pg/mL, p=0.03), and decreased IL-6 (12.5±15.4 to 8.6±11.3pg/mL, p=0.04).

**Conclusion**: Despite demonstrated prevention of NAFLD in animal models, nutraceutical trans-resveratrol at this dosage, over 8 weeks, did not demonstrate apparent clinical benefit in patients with well established NAFLD.