

# Pharmacometabolomic Signature Links Simvastatin

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## Introduction

Statins, widely prescribed drugs for treatment of cardiovascular disease, inhibit the biosynthesis of low density lipoprotein cholesterol (LDL-C). Despite providing major benefits, sub populations of patients experience adverse effects, including muscle myopathy and development of type II diabetes mellitus (T2DM) that may result in premature discontinuation of treatment. There are no reliable biomarkers for predicting clinical side effects in vulnerable individuals. Pharmacometabolomics provides powerful tools for identifying global biochemical changes induced by statin treatment, providing insights about drug mechanism of action, development of side effects and basis of variation of response.

## Objective

To determine whether statin-induced changes in intermediary metabolism correlated with statin-induced hyperglycemia and insulin resistance; to identify pre-drug treatment metabolites predictive of post-drug treatment increased diabetic risk.

## Methods

Drug-naïve patients were treated with 40 mg/day simvastatin for 6 weeks

in the Cholesterol and Pharmacogenetics (CAP) study; metabolomics by gas chromatography-time-of-flight mass spectrometry (GC-TOF-MS) was performed on plasma pre and post treatment on 148 of the 944 participants.

## Results

Six weeks of simvastatin treatment resulted in 6.9% of patients developing hyperglycemia and 25% developing changes consistent with development of pre-diabetes. Altered beta cell function was observed in 53% of patients following simvastatin therapy and insulin resistance was observed in 54% of patients. We identified initial signature of simvastatin-induced insulin resistance, including ethanolamine, hydroxylamine, hydroxycarbamate and isoleucine which, upon further replication and expansion, could be predictive biomarkers of individual susceptibility to simvastatin-induced new onset pre-type II diabetes mellitus. No patients were clinically diagnosed with T2DM. Conclusion Within this short 6 weeks study, some patients became hyperglycemic and/or insulin resistant. Diabetic markers were associated with decarboxylated small aminated metabolites as well as a branched chain amino acid directly linked to glucose metabolism and fatty acid biosynthesis. Pharmacometabolomics provides powerful tools for precision medicine by predicting development of drug adverse effects in sub populations of patients. Metabolic profiling prior to start of drug therapy may empower physicians with critical information when prescribing medication and determining prognosis.

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