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# CYP450 PHENOCONVERSION IN PATIENTS WITH TYPE 2 DIABETES: A MECHANISM FOR VARIABILITY IN DRUG RESPONSE

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**Background:** Type 2 diabetes (T2D) patients show highly variable responses to different drugs; some T2D patients appear resistant to certain drugs while being more sensitive to others. Therefore, we hypothesized that T2D and related inflammatory processes may alter expression and activities of major CYP450s involved in drug metabolism.

**Methods:** CYP450 activities were assessed in T2D patients (n=38) and healthy subjects (n=35) after an oral administration of a cocktail of CYP450 probe drugs consisting of 100mg caffeine (CYP1A2), 100mg bupropion (CYP2B6), 250mg tolbutamide (CYP2C9), 20mg omeprazole (CYP2C19), 30mg dextromethorphan (CYP2D6) and 2mg midazolam (CYP3A4/5). Metabolic ratios (MR) of AUC (drug/metabolite 0-8h) were determined. Proinflammatory cytokines, CYP450 genotypes, glycemia and insulinemia were measured.

**Results:** MRs of CYP2B6, CYP2C19 and CYP3As were considerably reduced in T2D vs non-T2D groups (1.5-2.5 fold, $p<0.01$). In opposite, CYP1A2 MR was higher in T2D patients ($p=0.003$) compared to non-T2D subjects. No phenoconversion was observed in T2D patients for CYP2D6 or CYP2E1. Proinflammatory cytokines explained ~8-23% of the variability in CYP450 activities.

**Conclusion:** Our study indicates that T2D affects CYP450s activities in an isoform specific manner. Our study demonstrates that T2D patients had a decreased metabolic activity of CYP3As, CYP2C19 and CYP2B6 which may lead to unintentional overdosing in T2D patients treated with substrates of these isoforms or lack of efficacy for certain pro-drugs.

### Biography

Veronique Michaud has received her Bachelor degree in Pharmacy in 2001 from Laval University, Quebec City and earned her PhD and MSc degrees from the Université de Montréal, Montreal, Canada. She has completed fellowship at McGill's AIDS Centre, Lady Davis Institute, McGill University, Montreal (2009-2010). She undertook a second fellowship in the department of Clinical Pharmacology, School of medicine, Indiana University, Indianapolis (2010-2012). She joined the University Of Florida College Of Pharmacy as an Associate Professor of Pharmacotherapy and Translational Research in January 2018. Prior to joining the UF College of Pharmacy, she served as the Vice President of scientific affairs at TabulaRasa Health Care in New Jersey. She was an Assistant Professor, Faculty of pharmacy, Université de Montréal from 2012 to 2016. Her research interests focus on Identifying Factors Responsible for Intersubject Variability in Drug Response. Her search investigates the contribution of CYP450 drug-metabolizing enzymes in drug disposition, with a special attention to the role of disease state, focusing on type 2 diabetes (T2D) in a CYP450 isozyme-selective and a tissue-selective fashion. One of the major focuses of her research is the Study of Intracellular Drug-Metabolism Leading to Modulation of Drug Action or Side Effects as well as the Role of Pharmacogenomics and Drug-Drug Interactions.

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