

NEWS

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CARDIOVASCULAR SIDE EFFECTS OF PIOGLITAZONE AND ROSIGLITAZONE LINKED TO VASCULAR AND ENERGY PATHWAYS BY GENOMAS CLINICAL STUDY

Basis Established for DNA-Guided Decision Support in Diabetes Drug Therapy

HARTFORD, CT – Research by Genomas and collaborators has shown statistically significant associations of certain genes in vascular and energy pathways to body mass index (BMI) and edema (fluid retention) in patients taking the thiazolidinedione (TZD) drugs pioglitazone (*Actos*[®]) and rosiglitazone (*Avandia*[®])*. The study, co-authored with investigators from Joslin Diabetes Center Affiliate at The Hospital of Central Connecticut, Hartford Hospital and Yale, appears in the February issue of the leading laboratory medicine journal *Clinica Chimica Acta*, published by Elsevier¹. The findings are being used to develop a DNA-guided decision support system for diabetic pharmacotherapy.

TZDs are powerful diabetes drugs currently utilized in patients failing first-line therapy with metformin and sulfonylureas. Patients given TZDs typically are at greater risk of diabetic complications and represent an advanced stage of the disease. However, TZDs have been observed to have side effects of weight gain and abdominal obesity, which exacerbate the diabetic condition itself, and to cause edema and exacerbate congestive heart failure in certain patients. Individuals vary in their risk and there is no known method for predicting such side effects. FDA-mandated “black box” warnings on the drug labels underscore the urgent need to better understand the mechanisms underlying these potentially serious side effects. Uncertainties surrounding the use of these drugs may place patients at risk, reduce patient compliance, burden medical management and increase healthcare costs.

The study involved a retrospective analysis of 87 patients taking either pioglitazone or rosiglitazone. A total of 384 single nucleotide polymorphisms (SNPs) from 222 cardiometabolic and neuroendocrine genes were selected and a physiogenomic analysis was performed. In physiogenomics, SNPs are correlated with physiological responses to provide information about which genes play a role in the process under study. Of the 384 SNPs tested, 25 showed statistically significant ($p < 0.05$) associations with BMI or edema. For BMI, the strongest associations were found with SNPs among genes involved in energy homeostasis, adiposity, glucose metabolism, and lipid metabolism. For edema, associations were found among the genes involved in vascular inflammation or regulation, lipid metabolism and glucose metabolism.

“For the first time in diabetic care, we can assess that genes in interlocking cardiometabolic and neuroendocrine pathways can be integrated into a PhysioType System, a multi-gene array and clinical model predictive of drug side effects,” said Gualberto Rúaño, M.D., Ph.D., President and CEO of Genomas, and Director of Genetics Research, Hartford Hospital. “Our existing PhysioType Systems for statin neuro-myopathy and antipsychotic-related diabetes are now being complemented by a third one for TZD-induced cardiovascular side effects for comprehensive DNA-guided medicine in modern healthcare.”

Diabetes represents a public health crisis with nearly 18 million people diagnosed in 2007, up from 11 million in 2000. An additional 6 million people have diabetes but have not been diagnosed (*CDC National Diabetes Fact Sheet, 2007*). Doctor visits for diabetes climbed from 25 million in 2001 to 36 million in 2007, and drug expenditures soared from \$7 billion to \$13 billion in the same time period.

“We are extremely pleased that our collaboration with Genomas is already yielding novel insight into diabetes drug therapy and are very confident that development of DNA-guided clinical management tool will result from it. There is an urgent public health need to improve the medical management of individuals on TZD therapy for their diabetes,” said Steven Hanks M.D., Chief Medical Officer at the Hospital of Central Connecticut, home of the Joslin Diabetes Center affiliate that participated in the study. “Using the patient’s personal genome for clinical decision support will be integral to evidence-based medicine and personalized healthcare.”

SCIENTIFIC BACKGROUND

Physiogenomics is a medical application of sensitivity analysis and systems engineering which defines a new paradigm in the genetic analysis of complex human phenotypes. Sensitivity analysis is the study of the dependence of a system on changes in its components. In physiogenomics, SNPs provide the variable components of genes, and analysis of the relationship between that variation and the physiological response provides information about which genes play important roles in the physiological process. The associated gene markers are combined into SNP ensembles harnessing their combined predictive power to estimate functional variability among individuals similarly treated.

In this study, physiogenomic associations were discovered suggesting mechanistic links between adenosine signaling and BMI, and between vascular permeability and drug-induced edema. The 5 most significant gene associations found between BMI and SNPs were *ADORA1* (adenosine A1 receptor), *PKM2* (pyruvate kinase-muscle), *ADIPOR2* (adiponectin receptor 2), *UCP2* (uncoupling protein 2), and *APOH* (apolipoprotein H). For edema, the 5 most significant gene associations were *NPY* (neuropeptide Y), *GYS1* (glycogen synthase 1-muscle), *CCL2* (chemokine C-C motif ligand 2), *OLR1* (oxidized LDL receptor 1), and *GHRH* (growth hormone releasing hormone).

ABOUT GENOMAS

Genomas[®] Inc. is a biomedical company advancing DNA-guided medicine and personalized healthcare. The company develops revolutionary PhyzioType[™] Systems for DNA-guided diagnosis and prevention of metabolic disorders induced by drugs used to treat diabetes, and cardiovascular and psychiatric illnesses. PhyzioType Systems are designed to provide physicians with an unprecedented capability to select for each patient the safest drug treatment to enhance compliance. Genomas is located in Hartford, CT on the campus of Hartford Hospital. Please visit www.genomas.net for more information.

ABOUT JOSLIN DIABETES CENTER AT THE HOSPITAL OF CENTRAL CONNECTICUT

The Joslin Diabetes Center Affiliate at The Hospital of Central Connecticut provides individualized care for people 18 and older with Type 1 or Type 2 diabetes, as well as pregnant women with diabetes. The Affiliate is housed at the New Britain General campus. The Hospital of Central Connecticut is a member of the Central Connecticut Health Alliance, a system of healthcare affiliates that provides a wide array of services throughout the region, caring for patients from birth through the end of life. Please visit www.thocc.org for more information.

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¹**BIBLIOGRAPHIC REFERENCE:** “*Physiogenomic Comparison of Edema and BMI in Patients Receiving Rosiglitazone or Pioglitazone*.” Gualberto Ruaño, James Bernene, Andreas Windemuth, Bruce Bower, Detlef Wencker, Richard L. Seip, Mohan Kocherla, Theodore R. Holford, William A. Petit, Steven Hanks. *Clinica Chimica Acta* 400: 48-55, 2009. The paper is available at www.genomas.net in the **Publications** section.

* *Actos*[®] is a registered trademark of Takeda. *Avandia*[®] is a registered trademark of GlaxoSmithKline.