Generating novel insights into the consequences of diabetes by integrating clinical, biomarker and genetic data in large cohorts

Dr Hertzel Gerstein is a Professor at McMaster University, Ontario, and at Hamilton Health Sciences. Dr Guillaume Paré is an Associate Professor in the department of Pathology and Molecular Medicine at McMaster. They are currently collaborating to generate novel insights into the consequences of diabetes by integrating clinical, biomarker and genetic data in large cohorts – with an aim to help clinicians prevent and treat heart disease, kidney disease, cognitive decline and other long-term consequences.

More than 750 million people worldwide have either impaired fasting glucose, impaired glucose tolerance or diabetes, and it is estimated that this number will continue to rise progressively in the foreseeable future. Compared to unaffected people, these dysglycaemic individuals suffer from premature cardiovascular disease, kidney disease, cognitive decline, premature mortality and a variety of other long-term health consequences. The subset with diabetes also experience impaired quality of life from the symptoms of high blood sugar levels as well as a higher risk of blindness, kidney failure, amputations and nerve damage than unaffected individuals.

WHY IS DYSGLYCAEMIA LINKED TO LONG-TERM SERIOUS HEALTH PROBLEMS?

There are several explanations for the adverse health consequences of dysglycaemia. Whereas most scientists agree that the prolonged exposure of tissue beds to elevated glucose levels is an important part of the explanation, the exact mechanism through which glucose causes damage and the role of the many metabolic abnormalities that are associated with the elevated glucose levels remains the focus of much research worldwide.

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THE ORIGIN OF GERSTEIN AND PARÉ’S COLLABORATION

Gerstein and Paré are currently analysing blood and genetic material obtained from a subset of participants in a recently completed international clinical trial called “ORIGIN” that was led by Gerstein and conducted between 2002 and 2012 in 12,537 people with dysglycaemia located in 40 countries. Published in 2012, the ORIGIN trial demonstrated that insulin has a neutral effect on serious health outcomes during more than six years of treatment. Their current collaboration focuses on the analyses of blood that was stored from a subset of 8,401 of these participants and the genetic material from a further subset of 5,000.

Analysis of the data has been for the following purposes: 1) to find biomarkers that can be used to identify and predict serious health outcomes – these need to be suitable for addition into routine medical data collection, and provide greater insight than current routinely collected data; 2) to find novel genetic variants that have been shown to cause cardiovascular problems (using a technique known as Mendelian randomisation); 3) to find novel biomarkers for already widely used medicines; and 4) to identify genetic and metabolic pathways that can lead to serious health problems and that may account for the benefit of some medications.

People with diabetes are twice as likely to develop heart disease or stroke compared to those who do not suffer from diabetes.
The identification of novel biomarkers can lead to new prognostic, diagnostic and therapeutic insights in people with dysglycaemia.

The identification of novel biomarkers and treatments work. Metformin is a drug whose mechanisms through which current drugs act are poorly understood. Unrecognised biomarkers for this drug and unrecognised biomarkers for other cardiovascular risk factors versus other cardiovascular risk factors?

What are the implications of your findings for the long-term treatment of dysglycaemia and diabetes?

By demonstrating a causal link between dysglycaemia and cardiovascular diseases, our findings suggest that early, long-term, intensive glucose lowering can reduce cardiovascular consequences and strongly support further clinical trials of the effect of safe glucose-lowering therapies.

The identification of novel biomarkers for serious health consequences will enable better discrimination of higher versus lower risk individuals so that clinicians can more precisely focus their therapies on people most likely to benefit.

What has been the most surprising result from your findings so far?

The identification of GDF15 as a very strong biomarker for metformin was surprising, and has opened up a new research focus in collaboration with Dr Gregory Steinberg.

What are the advantages of analysing genetic variants as cardiovascular risk factors versus other cardiovascular risk factors?

Genetic variants have the unique characteristic of being randomly distributed at conception among individuals (Mendel’s second law). They are also fixed throughout our lives. These features make it easy to separate the effect of genetic variants from other risk factors, and is one of the main advantages of including genetic information in biomarker studies.

What novelty does your method of combining genetic, clinical and biomarker data represent for research into diabetes and cardiovascular outcomes?

The unique analytic approach that we have developed and refined allows us to carefully separate genetic and/or biomarker associations with disease from those that are causally or mechanically involved in the development of the disease, to those that are confounded with measured or unmeasured causal factors.

What opportunities do you see presented by the age of ‘big data’?

The phrase ‘Big Data’ means different things to different people. From our perspective, it is both the development of careful, methodical analytic approaches and the application of these approaches to the large biomarker and genetic databases that are available, that yields robust, important findings that are relevant for both patients and health care providers.

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