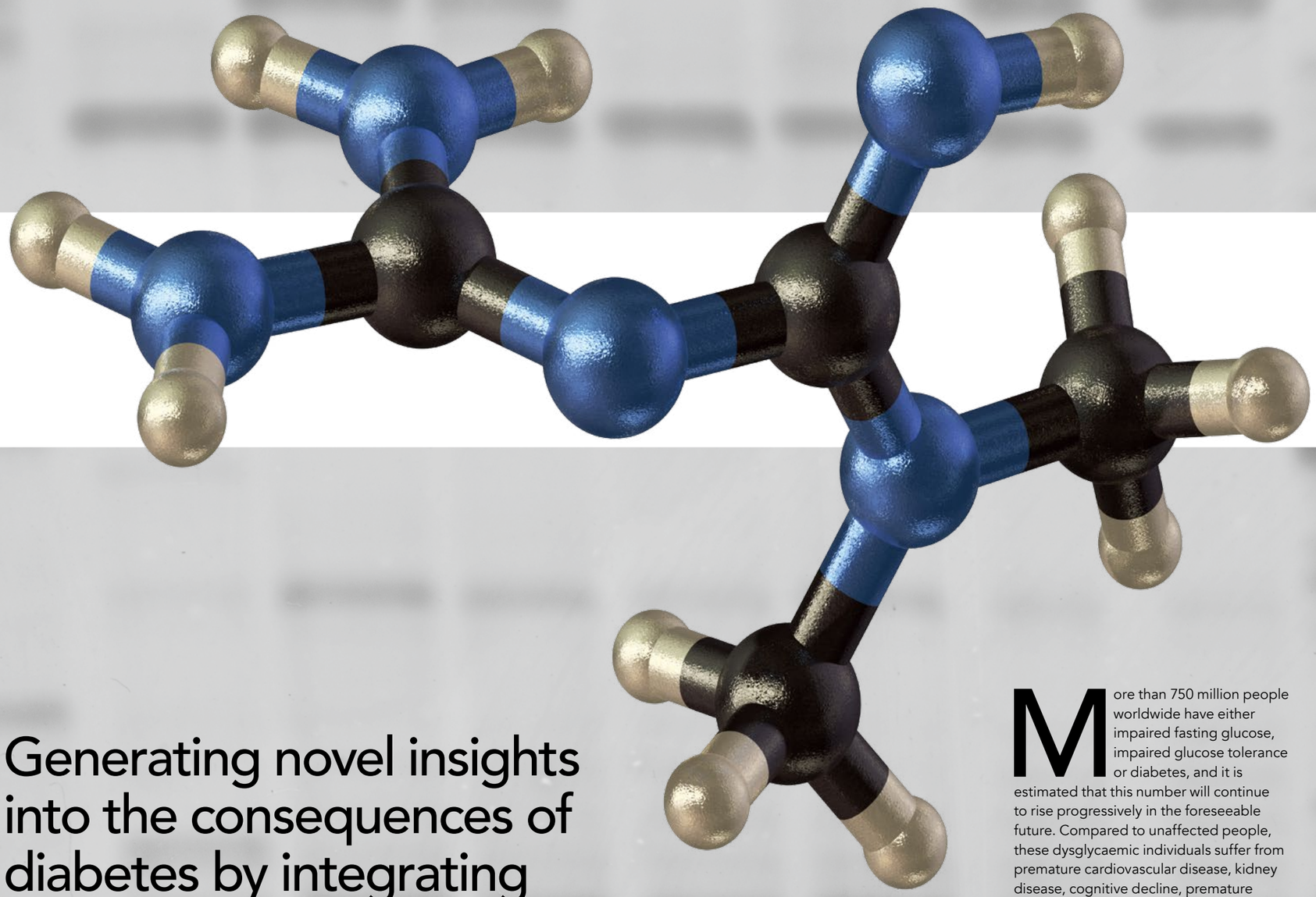

Generating novel insights into the consequences of diabetes by integrating clinical, biomarker and genetic data in large cohorts

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.

People with diabetes are twice as likely to develop heart disease or stroke compared to those who do not suffer from diabetes”

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.

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.

Analyses of this sort were made possible by the storage of samples in a large biobank located at the Clinical Research Laboratory in the Population Health Research Institute in Hamilton, Ontario, Canada, which contains samples from more than 250,000 participants who have participated in a large variety of studies over the last two decades. They are also made possible by new technologies that allow rapid and economical measurement of up to 1,500 different biomarkers in just 100 microlitres of blood and other technologies that facilitate comprehensive genetic analysis.

BIOMARKERS

A biomarker is any biological measurement or image that potentially contains information pertinent to the development, diagnosis, course or cause of a disease. Within diabetes, as in other diseases, the value of any one or set of biomarkers depends on how the data are acquired and analysed. For example, Gerstein, Paré and colleagues analysed a dataset of 237 biomarker levels that were measured in stored blood from each of the 8,401 ORIGIN participants. As this analysis was done prior to establishing the biomarker platform at the Population Health Research Institute, the measurement was done commercially (Myriad RBM Inc.). After conducting extensive statistical analyses of these data, Gerstein, Paré and colleagues were able to identify 15 unique biomarkers that individually and independently predicted death, and ten that individually and independently predicted cardiovascular

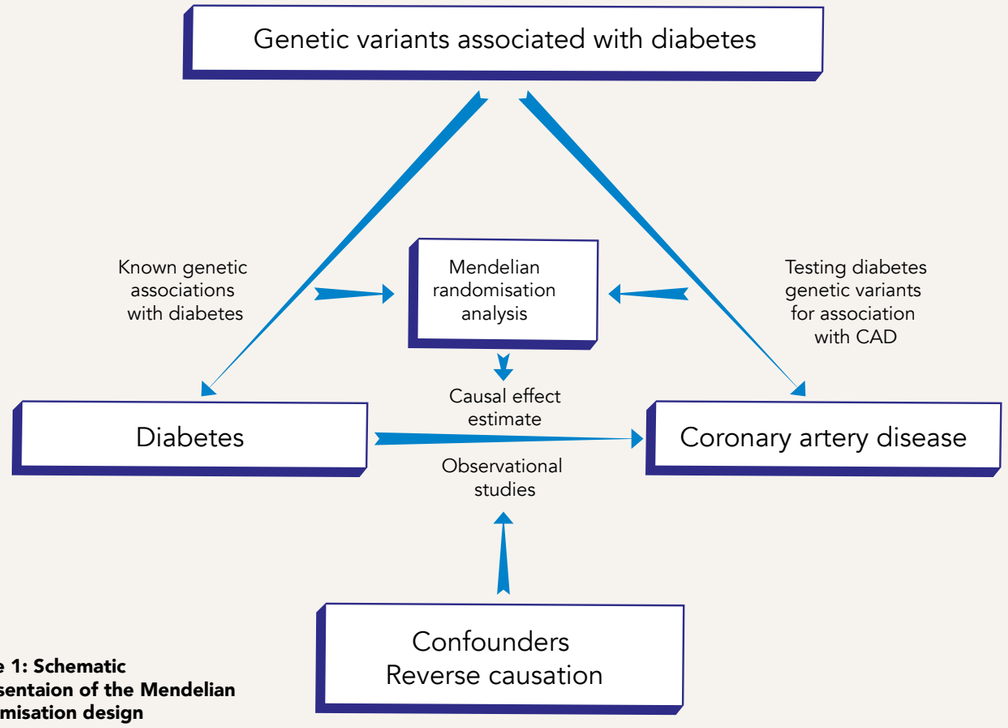

Figure 1: Schematic representaion of the Mendelian randomisation design

outcomes over a six- to seven-year period of time. The predictive ability of the identified panel of biomarkers was then confirmed in blood stored from other studies conducted by the Population Health Research Institute. Using a similar approach Gerstein and Paré further identified a related but somewhat different set of biomarkers that predicted eye or kidney disease (sometimes referred to as "microvascular outcomes") in the same individuals.

NEW BIOMARKERS FOR COMMON DRUGS

Biomarkers can also be used to test the mechanisms through which current drugs and treatments work. Metformin is a drug that is commonly used to lower blood glucose levels in people with diabetes, and that may also reduce mortality and cardiovascular diseases. The aim of Gerstein and Paré's research was to identify unrecognised biomarkers for this drug and to use these biomarkers to explore novel pathways for the drug's effect on serious health consequences.

26 biomarkers were independently associated with metformin use, but one of these jumped out as being up to four times more strongly linked than any of the others. This biomarker was Growth Differentiation Factor 15 (GDF15), which had also been strongly linked to cardiovascular outcomes in Gerstein and Paré's previous work. Using publicly available databases, they also found that genes that control the secretion of this biomarker may be linked to lower risks of cardiovascular outcomes.

Regulation of GDF15 expression and secretion remains unclear, but the strong link observed between metformin use and GDF15 suggests that metformin either enhances the secretion of GDF15 or reduces inhibitory pathways associated with it. The link between GDF15 and both metformin use and cardiovascular outcomes is of particular interest to them.

GENETIC VARIANTS

Gerstein and Paré have also used a technique called Mendelian randomisation to determine whether the well-documented statistical link between dysglycaemia and cardiovascular disease represents a causal relationship.

Mendelian randomisation is an analytic approach to genetics that is based on the fact that at the time of conception an individual randomly does or does not inherit genetic variants that increase the propensity to develop risk factors (e.g., high blood pressure or cholesterol) for a particular disease (e.g., heart disease). When done carefully, if the genetic variant that increases the level of risk factors for a disease is found to also increase the likelihood of developing the disease, it is strong evidence that the risk factor is in fact somehow causing the disease.

When they applied this approach to dysglycaemia, they found that glucose and HbA1c are both causally related to cardiovascular disease. They are currently applying this same approach to the 237 biomarkers identified in ORIGIN and together with publicly available genetic databases are discovering new causal biomarkers for cardiovascular disease.

THE DANGER OF JUMPING TO CONCLUSIONS

Gerstein and Paré only use very large datasets to conduct their analyses, to minimise the likelihood of anomalous or "chance" irreproducible results which are commonly seen when smaller datasets are used for biomarker discovery and related genetic analyses. Their collaborative work clearly demonstrates the prognostic and potentially therapeutic insights that can be gleaned from methodically analysing stored biologic material from large cohorts of people who have been carefully assessed and followed for the development of disease.

The identification of novel biomarkers can lead to new prognostic, diagnostic and therapeutic insights in people with dysglycaemia

Q&A

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 mechanistically 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.

Detail

RESEARCH OBJECTIVES

Dr Gerstein and Paré's collaborative research focuses on identifying novel serum and genetic biomarkers for cardiovascular and other serious long-term consequences of diabetes to both understand and reduce the likelihood of these consequences in people suffering from type 2 diabetes.

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COLLABORATORS

Population Health Research Institute and McMaster University in Hamilton Canada: Dr Matthew McQueen, Dr Shun Fu Lee, Dr Janice Pogue (deceased), Dr Gregory Steinberg, and Dr Salim Yusuf. Sanofi: Drs Heinz Haenel and Sibylle Hess

BIO

Dr Hertzel C Gerstein is an Endocrinologist and Professor at McMaster University and Hamilton Health Sciences, where he holds the Population Health Research Institute Chair in Diabetes. He is also Director of the Division of Endocrinology & Metabolism, Director of the Diabetes Care and Research Program and Deputy Director of the Population Health Research Institute and has had research published in over 300 papers.

Guillaume Paré is an Associate Professor at McMaster University and Director of the Genetic and Molecular Epidemiology Laboratory. He holds the Canada Research Chair in Genetic and Molecular Epidemiology as well as the CISCO Professorship in Integrated Health Biosystems. His research has been published in over 140 papers.

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