Insulin resistance, insulin action: Case Study

In 2017-18, almost 1 million Australian adults had type 2 diabetes and, in 2018, diabetes contributed to 11% of, or over 17,000, Australian deaths.[1,2] Cardiovascular disease is the primary cause of death for people with diabetes and obesity is a major contributor to the disease.[3] NHMRC-funded researchers at the Garvan Institute of Medical Research discovered key mechanisms in the causation of type 2 diabetes and its links with obesity and cardiovascular disease and provided key evidence that prevention primarily takes place through a healthy diet and lifestyle.

Origin

Diabetes, a medical condition characterised by high levels of blood glucose, causes a range of health problems. During the early 1920s, the first treatment for diabetes became available with the discovery and then mass production of insulin.

Insulin allows glucose to enter and provide energy for body cells. Insulin injection can help those people with diabetes who cannot produce their own. However, in 1950, NHMRC-funded researchers showed that some diabetic patients produced normal amounts of insulin.[4] This discovery, which underpins the current distinction between type 1 and type 2 diabetes (T2D), also revealed that those with T2D must have some other problem besides a lack of insulin.

This problem became known as 'insulin resistance' – a state in which glucose cannot enter body cells despite the presence of insulin. Insulin resistance was found to be closely connected with 'metabolic syndrome', a cluster of conditions – including obesity, high blood lipid levels and high blood pressure – that were themselves associated with an increased risk of cardiovascular disease and stroke.

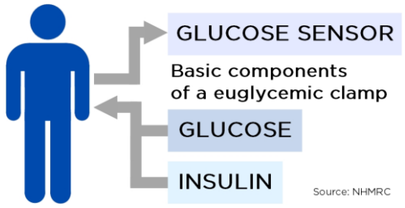
The causes of insulin resistance and their connections with metabolic syndrome were unclear. Understanding them became a focus for work in the Diabetes and Metabolism Program at the Garvan Institute of Medical Research, initiated during the 1960s by Professor Les Lazarus .

Source: iStock

Grants and Investment

NHMRC supported research at the Garvan Institute through Program and Block Grant funding (1982–2006), Equipment Grants and other grants. Other funding was provided by Kellion Foundation, Diabetes Australia, Beecham [later GlaxoSmithKline], AstraZeneca, Eli Lilly and NovoNordisk. This funding supported the work of a large and evolving team of researchers led by Don Chisholm and Ted Kraegen.

A key technique used by the team to investigate insulin resistance was the 'hyperinsulinemic - euglycemic clamp', which involved raising plasma insulin concentration (hyperinsulinemia) by a continuous infusion of insulin, while holding plasma glucose concentration constant at normal ('euglycemic') levels by a variable glucose infusion. Once a steady-state insulin infusion rate is achieved, the glucose infusion rate equals the net glucose uptake by all the tissues in the body and is therefore a measure of tissue insulin sensitivity.



Importantly, the team further developed this technique. By combining a custom-designed infusion apparatus and micro-sampling techniques with the use of radioactive glucose tracers they were able to find out where in the body (i.e. in which tissues) the insulin was acting. Before their work, there was little knowledge of this nor any effective means to obtain this information.

Research

Insulin action
Through use of the clamp and tracer technique, the Garvan Institute team found that:

- different tissue types – including cardiac muscle, skeletal muscle, brain, liver, and white and brown adipose (fat) tissue – all respond differently to insulin, and muscle is the most important target for insulin-mediated glucose storage when insulin levels are high
- glucose uptake occurs predominantly in skeletal muscles containing a high percentage of oxidative fibres, such as the diaphragm and the soleus (the large muscle on the back of the lower leg)
- the insulin dose/response relationship of skeletal muscles differs from that for cardiac muscle
- fat tissue – although previously thought to be an important destination for glucose disposal – makes only a minor contribution.

These findings showed that the effects of insulin in one tissue could not be extrapolated to other tissues in the body.

Insulin resistance
The team also found that:

- fat deposition in specific regions of the body, particularly around the viscera (internal organs), plays a key role in the development of insulin resistance, helping to explain the relationship between one component of metabolic syndrome (obesity, particularly in the abdomen) and insulin resistance
- muscle is the major location of insulin resistance in the body and insulin action in a muscle depends on the amount and type of fat in the muscle cells. However, liver cells accumulate fat much faster than muscle cells and fat accumulation parallels the development of insulin resistance in each type of cell.

Application

The Garvan Institute team made some significant discoveries about the management and treatment of diabetes. These included that:

- insulin-mediated glucose uptake into muscle can be enhanced by exercise and the enhancement is broader than those muscle groups specifically involved in the type of exercise employed
- muscle contraction is a much more potent stimulus of glucose uptake than is insulin in resting muscle
- high intensity intermittent exercise markedly increases fat oxidation, causes central abdominal fat loss and improves insulin sensitivity
- different types of fats either increase or decrease the level of insulin resistance and thus of T2D, and omega-3 unsaturated fats protect against insulin resistance in animals but not in humans
- insulin sensitivity improves with abdominal fat loss but, paradoxically, insulin resistance increases with loss of peripheral (hip and thigh) fat tissue
- abnormal fat metabolism is the major cause of dysregulated insulin action in diabetes and obesity
- central abdominal fat is strongly heritable, independently of total fat, explaining the apparent heritability of insulin resistance, T2D and cardiovascular disease
- obesity-related insulin resistance declines rapidly with reduced carbohydrate intake.

To increase T2D treatment options, the team examined pharmacological agents known as thiazolidinediones that could reduce lipids and enhance insulin sensitivity. Several of these agents became important in clinical practice.

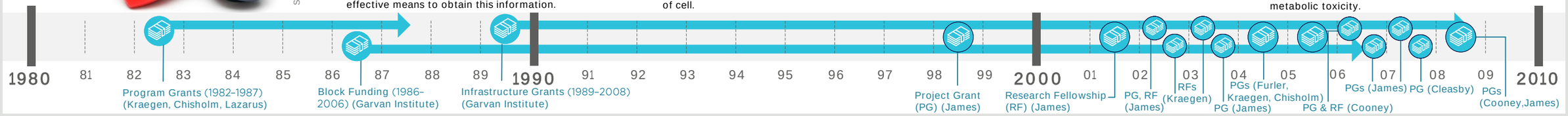
Health Outcomes and Impact

The Garvan Institute team established, for the first time, that a cause of insulin resistance was the accumulation of stored fat molecules in muscle and liver tissue and that interventions that reduced fat tissue accumulation – such as reducing dietary fat, altering the type of dietary fat consumed, increasing exercise and using pharmacological interventions – also lessened insulin resistance. Their research also explained the basic connection between T2D and metabolic syndrome.

The team's work made an early and important contribution to what became a steady flow of evidence that a modified fat or 'Mediterranean' diet is more effective for diabetes management than the high complex carbohydrate diet that was considered beneficial at the time.

Collaboration with Professor Stephen Boutcher from the Department of Exercise Physiology at the University of New South Wales (UNSW) also revealed the critical importance of high intensity intermittent exercise for fat loss in the management of T2D and obesity.

Professor David Cooper, Director of the Australian National HIV Centre, and colleague Dr Andrew Carr worked with Don Chisholm and Kathy Samaras at the Garvan Institute to understand fat tissue abnormalities, hyperlipidemia (elevated concentrations of fat in the blood plasma) and occasional diabetes in patients receiving medication for HIV. Together they identified an important new clinical syndrome – HIV Lipodystrophy Syndrome – in patients with HIV. Its symptoms included peripheral, but not abdominal, fat loss, sometimes also with areas of fat gain, and insulin resistance related to HIV antiviral therapy. Identification of the syndrome led to specific and successful efforts, supported by the pharmaceutical industry, to produce new HIV antiviral agents with less metabolic toxicity.



Note: NHMRC grants are dated by their start year

Prof Don Chisholm AO

Don Chisholm was head of the Garvan Institute's Diabetes and Metabolism Research Program (1978–2003) and Foundation Director of the Diabetes Centre at St Vincent's Hospital Sydney (1980–1991). Chisholm was appointed an Officer of the Order of Australia in 1999.

Prof Ted Kraegen AO

Edward (Ted) Kraegen became head of the Garvan Institute's Diabetes Research Group in 1990 and was Associate Professor and then Professor of Medicine at UNSW (1987–2009). Kraegen was appointed an Officer of the Order of Australia in 2019.

Prof David James

David E James undertook postdoctoral training at Boston University, held faculty positions at Washington University (USA) and at The University of Queensland, then led the Diabetes and Obesity Research Program at the Garvan Institute (2002–2014). He is now ARC Laureate Fellow and Domain Leader for Biology at the Charles Perkins Centre, The University of Sydney.

Dr Stuart Furler

Stuart Murray Furler (1949–2007) worked in Medical Physics at the Prince of Wales Hospital, Sydney, then at the Garvan Institute in the Diabetes Group (1982–2006).

Prof Leonard Storlien

Leonard Henry Storlien (1947–2022) was a researcher at the Garvan Institute (1982–1992), led a research group at Royal Prince Alfred Hospital, Sydney (1992–1994) and was Professor of Bio medical Sciences at the University of Wollongong (1992–2001), then Disease Area Scientific Leader – Obesity at AstraZeneca Sweden (2002–2006) and Leader – Obesity Research at the Boden Institute, The University of Sydney (2007–2019).

A/Prof Arthur Jenkins

Arthur B Jenkins worked at the Garvan Institute (1984–1995) and was then Associate Professor in Biomedical Sciences at the University of Wollongong.

Prof Gregory Cooney

Greg Cooney worked at Oxford University then Royal Prince Alfred Hospital, Sydney, before joining the Diabetes Group at the Garvan Institute in 1997. He was a Professor at UNSW and then a Professorial Research Fellow at the Charles Perkins Centre, The University of Sydney (2015–2012).

Prof Lesley Campbell AM

Lesley Veronica Campbell is Professor of Medicine, St Vincent's Clinical School, Faculty of Medicine, UNSW Sydney and was Director of the Diabetes Centre at St Vincent's Hospital, Sydney (1990–2014). She was appointed a Member of the Order of Australia in 2008.

Prof Jiming Ye

Jiming Ye is Chief Scientific Officer at Kunming Biomed International (KBI) in China. He worked at the Garvan Institute (1997–2010) and was Professor at RMIT University (2012–2021).

Dr Nicholas Oakes

Nicholas D Oakes worked at the Garvan Institute (1987–1997) and is currently Head of Preclinical Development for Cereno Scientific, Sweden.

Dr Mark Cleasby

Mark E Cleasby worked at the Garvan Institute (2002–2007) and was a Wellcome Trust Fellow at the Royal Veterinary College, London (2007–2014).

Other researchers

Prominent clinician researchers at an early stage of their careers contributed substantially to these research studies: Dr Mark Borkman, Prof David Bruce, Dr David Carey, Dr Simon Chalkley, Prof Seng Khee Gan, Prof Jerry Greenfield, Prof Tania Markovic, Dr Kerry Lee Milner, Dr Anne Poynten and Prof Kathy Samaras. In addition, significant contributions were made by a number of pre and postdoctoral scientists: Dr Kim Bell, Dr Michael Boden, Dr Amanda Brandon, A/Prof Clinton Bruce, Dr Bronwyn Hegarty, Dr Manthi Hettiarachchi, Dr Andrew Hoy, Dr Miguel Iglesias, Dr Diane Kriketos, A/Prof D. Ross Laybutt, Dr Swee Ng, Dr Alison Thompson and Prof Nigel Turner.

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References

This case study was developed with input from Professor Don Chisholm and Professor Ted Kraegen, and in partnership with the Garvan Institute of Medical Research.

The information and images from which impact case studies are produced may be obtained from a number of sources including our case study partner, NHMRC's internal records and publicly available materials.

The following sources were consulted for this case study:

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Partner

Garvan Institute of Medical Research