DIRECT
DIABETES RESEARCH ON PATIENT STRATIFICATION



You are what you eat….

Dr Rebeca Eriksen at Imperial College London explains their team's work on IMI DIRECT dietary data.

Professor Gary Frost and his team at Imperial College London have been investigating which foods and dietary patterns are important to help prevention and management of type 2 diabetes (T2D) in IMI DIRECT participants.

T2D is caused by many different factors with obesity, poor diet quality, physical inactivity and genetic factors being some of the main reasons. Diet is an important component and dietary advice remains one of the cornerstones of prevention and management of T2D by encouraging people to eat much more fruit, vegetables, wholegrains and dietary fibre, and decreasing added sugars and total fat intake.

Researchers at Imperial College investigated the dietary patterns of over 2,404 participants (1,818 pre-diabetic and 586 with T2D) from seven study centers around Europe: Malmo, Sweden; Copenhagen, Denmark; Exeter, Newcastle, Dundee (all UK); Kuopio, Finland and Amsterdam, The Netherlands. Diets were analysed using participants' recall of their food intake over the preceding 24 hours and the healthiness of their diet was measured against the World Health Organisation's dietary guidelines, which recommend a daily intake of at least 400g fruits and vegetables, 25g or more dietary fibre, max 30% total fats, max 10% saturated fat, max 10% sugars and a max 2500mg sodium (2.5g salt).

Our results showed the majority of the participants only met less than half of the six dietary guidelines. Participants eating the healthiest diet (i.e. they met at least four of the WHO's six recommendations) had a lower body weight: an average of 5kg less compared to those eating the worst diet (i.e. those who only met none to two of the dietary recommendations). They also had a smaller waistline and less deposits of liver fat, and most importantly better glucose and insulin control. Dietary benefits were also seen for people with T2D: those with the healthiest diets had 6% lower fasting glucose and 17% lower insulin compared to those with the worst diets. We also saw differences between the seven study sites. Participants with the best diets came from the study centre at Newcastle, UK and those with the worst diets were participants from Lund, Sweden.

This study sheds important light on why diet remains one of the most ripe areas for public health interventions for people at risk or already diagnosed with T2D. Our results show that with just a few simple dietary changes in your everyday life, you may help halt or even reverse your risk of T2D development.

What next for DIRECT?

Dr Ian Forgie, University of Dundee and Miranda Mourby, University of Oxford, discuss the arrangements in place to enable continued analysis of the DIRECT data and samples

After 7 years of collecting and analysing a huge amount of information (including clinical, molecular, biochemical, diet, exercise and MRI data!) from both diabetic and pre-diabetic people, the funding for the IMI-DIRECT project, which began in 2012, came to an end on 31 July 2019.

DIRECT was jointly funded by the European Commission (EC) as part of its Innovative Medicines Initiative (IMI) and is one of a number of public-private partnerships between the EC and various pharmaceutical companies who are members of the European Federation of Pharmaceutical Industries and Associations (EFPIA). In these partnerships the costs of a research programme are shared between the EC and EFPIA. (Other similar projects in the field of diabetes include SUMMIT and IMIDIA. Like DIRECT these have the common aim of bringing together leading experts from academia and industry to develop new solutions for improved disease management.)

Good progress has been made in analysing the data that has been gathered by DIRECT as can be seen in some of the scientific publications that have already been produced (see inside this Newsletter). However it is evident that a great deal more still needs to be done. Almost all of the project members are keen to continue their work investigating diabetes. This includes most of the universities, hospitals and companies who originally came together for the DIRECT project.

The good news is that four of the EFPIA partner companies — Sanofi-Aventis, Eli Lilly, Novo Nordisk and Boehringer Ingelheim— have kindly agreed to fund the cost of keeping a skeleton infrastructure in place over the next 2 years in order to enable analyses to continue, so that we extract as much value and benefit from the data as we can. Their funding is critical in helping cover the costs of maintaining access to the DIRECT database in Denmark as well as the sample collection held at Exeter and the coordinating functions performed by Dundee in the UK. Thus, the data will remain in Denmark for at least 2 years, allowing analysts in this "DIRECT Legacy Consortium" much needed time to investigate and evaluate the huge amount of information that has been collected, and generated through scientific tests, as well as to assess what it reveals. Potentially, it will also allow other diabetes researchers the opportunity to collaborate with us in these investigations. We hope this will enable us to make high-impact discoveries about the causes of diabetes, and how it can best be treated in different people.

Your data, such as the results of your tests, will continue to be stored on a secure server, which is owned and operated by the Technical University of Denmark ('DTU') and overseen by the project members. As always, this 'clinical' information in DTU will not include your personal details such as your name, address or hospital number. Your personal information will only be kept by the hospital you attended for as long as you gave them permission to keep it.

It is very important that we use your information ethically and in line with the law such as the new General Data Protection Regulation. You will have rights under this regulation about any information which relates to you, although in the case of scientific research there may be some exceptions (for example, we may not be able to delete data which has already been used in an analysis). There is information about the GDPR on the following webpage: https://www.direct-diabetes.org/information/#gdpr .

We will always comply with the terms of your original consent as we continue to use your clinical information. We will also set strict data security standards, and only allow access to limited information for genuine research into diabetes and related conditions. If you have any questions about your data, please contact Dr Ian Forgie (see page 1) or your recruitment centre (for details, go to the project website https://www.direct-diabetes.org/information/ and click on 'Clinical Study Centres').

Although the EU funding has now finished, members of the DIRECT project are still highly committed to using your data and samples for the purpose for which you provided them: ground-breaking research into diabetes!

Final DIRECT scientific meeting held in Scotland 21-23 May 2019


DIRECT Researchers at the Plenum in Crieff, Scotland

DIRECT researchers from around Europe met at a hotel in the southern highlands of Scotland in the early summer to present their work on type 2 diabetes (T2D) and to discuss each other's findings. They were joined by members of DIRECT's Scientific Advisory Board, which includes diabetes experts from the US and elsewhere.

In a packed programme held over two days delegates were able to hear first-hand from colleagues on the progress being made in analysing the large quantity of data that has been accumulated by the DIRECT Consortium; they were able to discuss together what the findings suggested and identify the areas that require more investigation and analysis.

Topics ranged from how T2D varies in different individuals, to the molecular and biochemical characteristics of different groups of patients, to the response of patients to different treatments. The impact of diet, the distribution of body fat and topics such as identifying which individuals may benefit most from bariatric surgery were all covered. Further details on some of these topics is provided elsewhere in this Newsletter. A keynote address on 'Precision medicine in T2D' was given by Prof Jose Florez from Harvard University who indicated how impressed he was with the DIRECT project and the level of detailed assessment that had been conducted on each participant and on the samples that have been collected.


Prof Jose Florez, who led DIRECT's external Scientific Advisory Board, giving a talk at the Plenum

Any Questions?

If you have any questions related to the DIRECT Project, including about your data, the initial point of contact is:

Dr Ian Forgie, University of Dundee
(*email*: i.m.forgie@dundee.ac.uk)

Keep in touch!

'The Direct Project'

@DIRECTdiabetes

http://www.direct-diabetes.org/information

RESEARCH ROUND-UP

Here are the latest updates from a number of our study teams throughout Europe

Sensitivity to insulin, insulin production and other factors affect how quickly diabetes progresses

DIRECT investigators Roberto Bizzotto and Andrea Mari, CNR Neuroscience Institute, Padova, Italy, reveal the mechanisms that affect the progression of type 2 diabetes

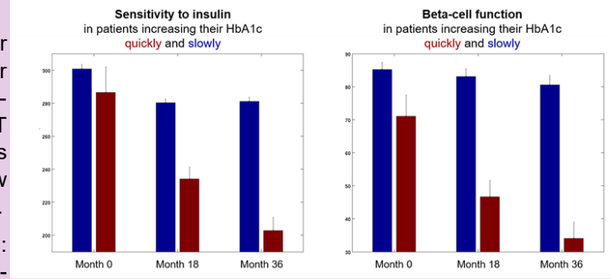
Type 2 diabetes occurs when you have a persistent increased level of sugar (glucose) in the blood. Maintaining the glucose level as low as possible in diabetic patients is important in order to avoid the complications that the disease causes. In spite of lifestyle changes and taking medication, glucose levels can worsen with time at a slow or at a fast rate for reasons that are not yet clear. Understanding the disease mechanisms that underlie these different progression rates may be important for better, individualized treatment.

DIRECT investigators monitored deteriorating blood sugar levels in patients by measuring their glycated haemoglobin, or "HbA1c". This gives an indication of a person's average glucose levels during the past several weeks. In the DIRECT study, HbA1c was measured in diabetic patients multiple times over 3 years, to estimate its rate of change, and gauge how fast each patient's blood sugar was improving or deteriorating.

Two main questions have concerned DIRECT investigators: which chemical, biological or clinical features predict an individual's rate of progression? And secondly, what are the physiological mechanisms behind the different rates of progression in the patients? These issues were investigated by DIRECT, and the preliminary results are very interesting.

DIRECT investigators have found new clinical traits, measured at the first visit, which independently predict a more rapid increase in HbA1c in the following years. These traits are: lower age, a fattier liver, a lower sensitivity to insulin (i.e. reduced ability of muscles and fat to use glucose when stimulated by insulin), and a reduced beta-cell function (i.e. the ability of the beta cells of the pancreas to produce insulin is impaired). Insulin sensitivity is known to be strongly related to obesity, so that obese patients tend to experience a quicker deterioration in their diabetic state than lean patients. The effect of age was already known, but the role of liver fat and of the health of the pancreas, muscles and whole-body fat tissue is a new finding.

Analysis of progression data also revealed that patients whose HbA1c increased more quickly are those showing, over time, a quicker increase in triglycerides (blood fat levels) or ALT (a liver enzyme), or a quicker decrease in sensitivity to insulin or beta-cell function (see figure below). Among these different factors, the role of variation in insulin sensitivity and beta-cell function was the strongest, which highlights the importance of the biological mechanisms taking place in muscles, fat and pancreas, in the control of blood glucose concentration. Further studies are thus required to understand the reasons for the worsening of these parameters and how the deterioration can be slowed down.

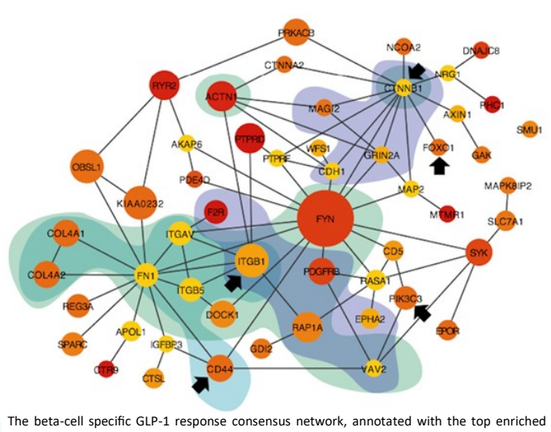


The results of this study were presented at the main annual Diabetes meeting in Europe (EASD) in September 2019.

Genes play a role in insulin secretion stimulated by the hormone GLP-1

Dr Valborg Guðmundsdóttir formerly of DTU, Copenhagen gives a brief description of her recent GLP-1 paper

Certain types of anti-diabetic drugs, such as "Glucagon-like petide-1 (GLP-1) receptor agonists" and "DPP4-inhibitors" are designed to increase the secretion of insulin by beta cells in the pancreas. They do this by increasing the levels of a hormone called "GLP-1". However, the response to these drugs varies considerably between individuals. This may partly be explained by people's genetic differences. In DIRECT we therefore sought to identify genetic differences between individuals that have an influence on the response to GLP-1. We performed a genetic study of 126 Dutch non-diabetic individuals who were injected with GLP-1. Their level of insulin secretion was then measured. As this is a time-consuming and costly measurement only a small number of people could be studied and too few to identify clear genetic associations. However, focusing on genes that affect the pancreatic beta-cells, we found that many suggestive genetic associations fell within a small network of genes that interact with each other. Genes that are connected in such a network are generally involved in the same biological processes. The study highlighted a set of candidate genes and biological pathways that are likely to be involved in an individual's response to GLP-1. This needs to be confirmed and explored further in future studies. The diagram gives an illustration of the complexity of the biological interactions that we are trying to understand.



The beta-cell specific GLP-1 response consensus network, annotated with the top enriched KEGG pathways: Focal adhesion (green), ECM-receptor interaction (blue) and Rap1 signaling (purple). Arrows indicate genes that were identified as upstream regulators of differentially expressed genes in the transcriptome analyses of the liraglutide treated mice versus baseline controls.

https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0189886

Some scientific publications emerging from DIRECT

Title	Author(s)	Internet Reference
Discovery of biomarkers for glycaemic deterioration before and after the onset of type 2 diabetes: rationale and design of the epidemiological studies within the IMI DIRECT consortium	Koivula R et al.	Diabetologia. 2014 Jun; 57(6):1132-42. doi: 10.1007/s00125-014-3216-x.
Discovery of biomarkers for glycaemic deterioration before and after the onset of type 2 diabetes: descriptive characteristics of the epidemiological studies within the IMI DIRECT Consortium	Koivula R et al.	Diabetologia. 2019 Jun 15. doi: 10.1007/s00125-019-4906-1
Gene × physical activity interactions in obesity: combined analysis of 111,421 individuals of European ancestry	Ahmad S et al.	PLoS Genetics. 2013; 9(7):e1003607. doi:10.1371/journal.pgen.1003607.
Gene-environment and gene-treatment interactions in type 2 diabetes: progress, pitfalls, and prospects	Franks PW, Pearson E, Florez JC	Diabetes Care. 2013 May; 36(5):1413-21. doi: 10.2337/dc12-2211.
Weight loss independent association of TCF7L2 gene polymorphism with fasting blood glucose after Roux-en-Y Gastric Bypass in type 2 diabetes patients	Rouskas K, Cauchi S, Raverdy V, Yengo L, Froguel P, Pattou F	Surg Obes Relat Dis. 2014 Jul-Aug;10(4):679-83. doi: 10.1016/j.soard.2013.12.016
Causal inference in obesity research	Franks PW, Atabaki-Pasdar N	J Intern Med. 2016 Dec 8. doi: 10.1111/joim.12577.
Lifestyle and precision diabetes medicine: will genomics help optimise the prediction, prevention and treatment of type 2 diabetes through lifestyle therapy?	Franks PW, Poveda A.	Diabetologia. 2017 May; 60(5):784-792. doi: 10.1007/s00125-017-4207-5
Exposing the exposures in type 2 diabetes	Franks PW & McCarthy MI	Science. 2016 354(6308):69-73.
Sustained influence of metformin therapy on circulating glucagon-like peptide-1 levels in individuals with and without type 2 diabetes	Preiss D et al	Diabetes Obes Metab. 2017; 19(3):356-363. doi: 10.1111/dom.12826.
Predicting glycated hemoglobin levels in the non-diabetic general population: Development and validation of the DIRECT-DETECT prediction model - a DIRECT study	Rauh SP et al	PLoS One. 2017 Feb 10; 12(2):e0171816. doi: 10.1371/journal.pone.0171816
Personalized medicine in diabetes: the role of 'omics' and biomarkers	Pearson ER	Diabet Med. 2016 Jun; 33(6):712-7. doi: 10.1111/dme.13075.
Painting a new picture of personalised medicine for diabetes	McCarthy M	Diabetologia. 2017 Feb 7. doi: 10.1007/s00125-017-4210-x.
Integrative network analysis highlights biological processes underlying GLP-1 stimulated insulin secretion: A DIRECT study	Guðmundsdóttir V et al	PLoS One. 2018 Jan 2; 13(1):e0189886. doi: 0.1371/journal.pone.0189886
A Genome-Wide Association Study of IVGTT-Based Measures of First-Phase Insulin Secretion Refines the Underlying Physiology of Type 2 Diabetes Variants	Wood AR et al, including Diabetes Research on Patient Stratification (DIRECT)	Diabetes. 2017 Aug; 66(8):2296-2309. doi: 10.2337/db16-1452.
Metabolite ratios as potential biomarkers for type 2 diabetes: a DIRECT study	Molnos S, Wahl S, Haid M et al	Diabetologia. 2018 Jan; 61(1):117-129. doi: 10.1007/s00125-017-4436-7
Type 2 diabetes: a multifaceted disease	Pearson ER	Diabetologia. 2019; 62(7): 1107–1112. doi: 10.1007/s00125-019-4909-y
Evidence-based prioritisation and enrichment of genes interacting with metformin in type 2 diabetes	Dawed AY et al	Diabetologia. 2017; 60(11): 2231–2239. doi: 10.1007/s00125-017-4404-2
The governance structure for data access in the DIRECT consortium: an innovative medicines initiative (IMI) project	Teare HJA et al	Life Sci Soc Policy. 2018 Dec; 14:20. doi: 10.1186/s40504-018-0083-0
Rates of glycaemic deterioration in a real-world population with type 2 diabetes	Donnelly LA et al	Diabetologia. 2018; 61(3): 607–615. doi: 10.1007/s00125-017-4519-5
Motivations for data sharing-views of research participants from four European countries: A DIRECT study	Shah N et al	Eur J Hum Genet. 2019 May; 27(5):721-729. doi: 10.1038/s41431-019-0344-2.

Predicting diabetes remission after weight loss surgery

Dr François Pattou and colleagues at the University Hospital of Lille in France look into the effects of weight loss surgery on obese individuals with type 2 diabetes.

Roux-en-Y stomach bypass surgery is the most common type of surgical procedure and involves reducing the size of the stomach by 90% (so restricting food intake) and reconnecting the remaining stomach pouch to a section of the small intestine called the jejunum. Food thus "bypasses" digestion in the stomach and the upper portion of the small intestine. The operation results in significant weight-loss and causes remission (i.e. reduction or disappearance of signs and symptoms of the disease) of type 2 diabetes in 80 percent of patients and improvement of the disease in an additional 15 percent of patients. Thus gastric bypass surgery is an active area of research.

As part of the DIRECT research program, 250 obese individuals (BMI > 35) kindly agreed to participate in a study and were followed-up for one year after Roux-en-Y bypass surgery. Alongside their clinical data, we collected blood, adipose (fat) and liver tissues samples during surgery (see figure). The latest technologies were employed to analyze and integrate the data generated by the European DIRECT consortium. Exploring this unprecedented data set with artificial intelligence techniques allowed us to identify several markers (i.e. genes, proteins, lipids) specifically associated with remission of a patient's diabetes after undergoing Roux-en-Y bypass surgery. Overall, our data demonstrated the value of using multiple markers to identify those patients who are likely to benefit most from surgically induced diabetes remission.

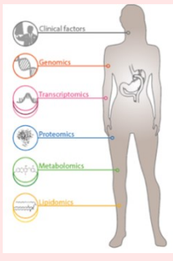


Fig 1. Data for each patient include routine clinical data and other markers: genes, proteins, lipids from blood and tissues (liver, subcutaneous fat and visceral fat)