Report of the European Group for the Study of Insulin Resistance annual meeting, Dublin, 4–6th May 2017

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The annual meeting of the European Group for the study of Insulin Resistance (EGIR) was held in Dublin, Ireland in May 2017. Ably organized by Dr. Mesud Hatunic, Consultant Endocrinologist at Mater Misericordiae University Hospital, the conference explored the pathophysiology and treatment of insulin resistance and extended a perspective to include aspects of clinical diabetes care including diabetic retinopathy (Dr. David Keegan, Consultant Vitreo-Retinal Surgeon, Mater University Hospital, Dublin, Ireland), monogenic forms of diabetes (Dr. Maria Byrne, Consultant in Endocrinology and Diabetes, Mater Misericordiae Hospital, Dublin, Ireland) and the impact of gastric bypass surgery (Professor Carel le Roux, Co-Director of the Metabolic Medicine Group, University College, Dublin, Ireland). The group actively welcomed the participation of members who have recently joined from the Pasteur Institute in Lille, France, including Dr. Caroline Bonner, who will co-host the Spring 2018 EGIR meeting there with Professor Francois Pattou. New members are always welcome, e-mail: egir@med.unipi.it for details.

Here, we present brief summary highlights of some of the invited lectures from the conference.

Dr. David Savage: Wellcome Trust Senior Clinical Fellow, Department of Clinical Biochemistry, University of Cambridge, Cambridge, UK

What has lipodystrophy taught us about insulin resistance?

Dr. Savage's laboratory focuses on the molecular basis of insulin resistance in humans. In his lecture, Dr. Savage explored insights into impaired insulin action that have been gleaned from lipodystrophy syndromes. By way of introduction, white adipose tissue serves to buffer excess energy by sequestering fatty acids; energy substrate in the form of fatty acids is then released, as required, through the process of lipolysis in which triglycerides are hydrolysed to fatty acids and glycerol. Excess adiposity (overweight and obesity) is a well-established driver of insulin resistance, glucose intolerance and type 2 diabetes. During the 1990s, it was shown that WAT-derived inflammatory mediator tumour necrosis factor- α participates in obesity-related systemic insulin resistance by

inhibiting the tyrosine kinase action of the transmembrane insulin receptor together with impaired phosphorylation of insulin receptor substrate-1 in muscle and fat tissues. Death of white adipocytes is associated with a local inflammatory response. Macrophages infiltrating the adipose tissue of obese animals and humans are arranged around dead adipocytes to form characteristic crown-like structures. Although inflammation within adipose tissue is not necessarily required for insulin resistance, it may exacerbate defects in insulin action. The role of macrophage infiltration into white adipose tissue in causing inflammation remains uncertain, with current evidence providing inconsistent support for a causal effect. Insulin resistance can develop in the absence of adipose tissue inflammation in animal models. Obesity is associated with elevated plasma concentrations of nonesterified fatty acids and proinflammatory cytokines, along with endoplasmic reticulum and oxidative stress that have been shown to induce insulin resistance. However, current evidence suggests that acute overfeeding (6000 kcal/day), while rapidly inducing whole-body insulin resistance, does not induce inflammatory stress.

Paradoxically, both excess (obesity) and deficient (lipodystrophy) fat lead to adipose tissue dysfunction, ectopic lipid accumulation, insulin resistance and diabetes. Intriguing parallels between adiposity and the syndromes of complete and partial lipodystrophy (in which subcutaneous fat deposits are markedly reduced) have long been appreciated.

Dr. Savage suggested that the view of adipose tissue as an endocrine organ has perhaps been somewhat overstated. For example, is adiponectin appropriately considered to be a classic hormone? He proposed that, in the context of obesity-associated metabolic disease, there should be a refocus on the adipocyte's role in lipid storage. White adipose tissue plays an important role in regulating energy flux for the metabolic benefit of higher organisms. Even lean individuals have 100-fold more energy stored as lipid versus carbohydrate. Triglyceride and cholesterol esters are stored in a single large droplet. This reduces the lipid droplet surface area available to lipolytic enzymes and optimizes storage capacity. If obesity exceeds the ability of adipose tissue to store and

handle excess energy supply, adverse metabolic consequences may result.

Lipodystrophies reflect either the failure of adipocyte development or premature destruction of adipocytes because of genetic or immunological mechanisms. Dr. Savage reviewed the genetic basis of inherited lipodystrophy syndromes including novel mutations identified in his laboratory. These include a patient with multi-loculated lipid droplets and insulin-resistant diabetes who was found to be homozygous for a premature truncation mutation in the lipid droplet protein cell death-inducing Dff α -like effector C. Other genetic causes identified by University of Cambridge researchers include mutations of LMNA encoding the *lamin A/C* gene in partial lipodystrophy.

Hyperphagia has been described in some syndromes and also in mouse models of lipodystrophy. Dr. Savage touched on potential methodological issues relating to animal studies of fat metabolism in which mice are effectively subjected to cold stress under standard laboratory conditions instead of being studied in an appropriately thermoneutral environment.

Dr. Savage proposed that subtle forms of lipodystrophy are a prevalent cause of insulin resistance and type 2 diabetes. Individuals who have a higher fat storage capacity have a metabolic advantage at higher levels of body mass index than individuals without such genetic variation. Genome-wide association studies suggest that genetically determined lower gluto-femoral fat storage may lead to overspill of lipid into visceral stores with insulin resistance and dyslipidaemia. Conversely, alleles associated with relative gynoid obesity (high thigh girth, thigh fat, hip circumference) in women appear to confer systemic insulin sensitivity. The hypothesis that stratified risk identifies individuals who would be more likely to benefit from interventions such as bariatric surgery merits testing.

Professor Jules Griffin: Professor of Metabolism and Nutrition, Department of Biochemistry, University of Cambridge, Cambridge, UK

Triglycerides and diglycerides in the Fenland cohort

Metabolomics has been described as representing a paradigm shift in metabolic research that moves away from approaches that focus on a limited number of enzymatic reactions or single pathways to approaches that attempt to capture the complexity of metabolic networks. In his lecture, Professor Griffin presented an accessible review of metabolomics and lipidomics as tools in the investigation of the metabolic syndrome. Professor Griffin's studies focus on stratification of patients by the risk factors that are considered integral to the metabolic syndrome, the Fenland cohort.

Professor Griffin presented an overview of the methodologies and their application in metabolic disorders such as identifying novel biomarkers of insulin resistance as an aid to drug discovery, defining drug toxicity and predicting the development of nonalcoholic fatty liver disease in the Fenland cohort study. It is now possible to profile the individual triacylglycerols (triglycerides) in blood plasma or tissue extracts in cardiometabolic diseases as well as the development of insulin resistance and obesity.

With respect to metabolomics, Professor Griffin described the analytical in terms of pattern recognition used to define metabolism in a multidimensional space. Pattern recognition can be unsupervised, that is, exploratory or hierarchical cluster analysis using principal components analysis or supervised with external correlates. Issues include the large mass range and polarity of molecules and nanomolar concentrations of (10^9) small molecule metabolites. The complexity of the task is illustrated by the lipidome, which alone comprises ~8000 molecular entities; these challenges require a multiplicity of laboratory approaches. High-throughput technology in Professor Griffin's laboratory can process 2000 samples per week at two parts per million discrimination.

Early metabolomic studies indicated potential aminoacid and lipid biomarkers associated with insulin resistance and diabetes. However, although many biomarkers have been reported to be associated with the risk of developing type 2 diabetes, the evidence of their value in adding to understanding of causal pathways to disease generally remains rather limited. Nonetheless, valuable mechanistic insights into the pathophysiology of the metabolic syndrome have been gained from elegant clinical metabolic studies carried out by Professor Griffin's colleague Dr. David Savage in which the metabolic profiles of subtypes of insulin resistance were examined. In one subtype, the molecular defect in insulin action was known to reside at the insulin receptor because of loss-of-function insulin receptor mutations or inhibitory antibodies directed towards the insulin receptor. Increased de novo lipogenesis is a feature of lipodystrophy syndromes, but not of defects in insulin signalling at the level of the transmembrane insulin receptor. Thus, the alterations in lipid metabolism arising from postreceptor defects in patients with lipodystrophy are manifested in increased lipogenesis, elevated liver fat content, triglyceride-enriched very-low density lipoproteins, hypertriglyceridaemia and low levels of high-density lipoprotein cholesterol. In contrast, insulin resistance arising as a consequence of lipodystrophy was associated with a lipid pattern similar to metabolic syndrome, that is, hypertriglyceridaemia and reduced levels of high-density lipoprotein-cholesterol. A similar pattern was observed in patients with a selective postreceptor defect in the downstream protein serine–threonine kinase AKT2. The key seems to be which organ – liver versus muscle – is

preferentially affected by the insulin signalling defect, and where along the path of lipid metabolism the insulin signalling defect operates. Low rates of hepatic de novo lipogenesis in the absence of steatosis were observed in the insulin receptor syndromes. The distinction between these rare forms of molecularly characterized forms of insulin resistance suggests that partial postreceptor hepatic insulin resistance is a key factor in the development of metabolic dyslipidaemia and hepatic steatosis.

Professor Finbarr O'Harte: Professor of Endocrinology and Metabolism, The Saad Centre for Pharmacy and Diabetes, Ulster University, Coleraine, UK

Assessment of the therapeutic potential of peptide mimetics for alleviating metabolic dysfunction in diabetes and obesity

Professor O'Harte's laboratory focuses on the development of stable analogues of regulatory peptides including glucose-dependent insulintropic peptide, glucagon-like peptide-2, cholecystokinin, glucagon and apelin. In a witty and informative presentation, Professor O'Harte presented data from his laboratory on apelin – a 13 amino acid with a range of cardiometabolic actions. Apelin is credited with cardioprotective properties including lowering of blood pressure. The brain, gut and kidney are also included in the extended list of organs in which apelin has regulatory effects. The apelin receptor (APJ receptor) is expressed in pancreatic islets and apelin activation through its receptor inhibits insulin secretion. Synthetic apelin–fatty acid conjugates have been synthesized that increase the half-life of the peptide. In-vitro studies using the pancreatic BRIN-BD11 glucose-responsive insulin-secreting cell line – developed by Dr. O'Harte and colleagues – and in-vivo experiments have shown stimulation of insulin secretion, lowering of plasma glucose, improved lipid profiles, improved insulin sensitivity, reduced energy intake, body weight reduction and RAS inhibition. Thus, apelin analogues appear to offer a promising novel therapeutic approach for diabetes and obesity.

Dr. Diamuid Smith: Consultant Endocrinologist, Baumont Hospital, Dublin, Ireland

On the TRAIL of a biomarker for cardiovascular disease

Why is it that with age, the calcium content of the skeleton tends to decline, whereas calcium deposits start to appear in vascular tissue? Although bone and vascular tissues seem disparate and at first sight unconnected, there is more overlap than perhaps is widely appreciated. Ectopic arterial mineralization is frequently accompanied by decreased bone mineral density. This contradictory association, observed mainly in osteoporosis and chronic kidney disease, has been called the 'calcification paradox'. Vascular calcification comprises two main types:

media and intima. Vascular calcification, including calcific aortic valve disease, correlates with features of metabolic syndrome, obesity, diabetes mellitus, chronic kidney disease, hypertension and chronic inflammation. To endocrinologists, vascular calcification is well recognized in the clinical setting as incidental medical calcification on plain radiographs in patients with diabetes of long duration and/or advanced renal disease. Although vascular calcification portends cardiovascular morbidity and mortality, its presence should not be considered synonymous with atherosclerosis.

Dr. Smith offered a review of bone-regulatory proteins including osteoprotegerin (OPG) and receptor activator for nuclear factor- κ B ligand, and tumour necrosis factor-related apoptosis-inducing ligand. These newly discovered members of the tumour necrosis factor- α receptor superfamily have attracted attention as possible mediators of bone–vascular calcification imbalance. However, their physiological functions within the vasculature remain incompletely understood. OPG inhibits vascular calcification *in vitro* and high serum levels of OPG have been found in patients with type 2 diabetes. Positive correlations have been described between OPG and interleukin-6, whereas no correlations have been found between RANKL or TRAIL and markers of inflammation, that is, high-sensitivity C-reactive protein or interleukin-6. TRAIL levels are reduced in newly diagnosed patients with type 2 diabetes.

Levels of OPG correlate with the severity of vascular calcification. OPG is released by vascular damage and circulating levels correlate with pulse wave velocity (PWV). In men with type 2 diabetes, atorvastatin reduced circulating OPG and PWV, the latter being an indirect measure of arterial stiffness. The correlation observed between reductions in PWV and OPG suggests that atorvastatin may reduce PWV by direct anti-inflammatory effects on the vasculature.

Professor Carel le Roux: Metabolic effects of gastric bypass surgery, Head of pathology Department of Pathology, University College Dublin, Dublin, Ireland

Prof Carel le Roux presented a fascinating and enthusiastic account of his cutting-edge work on the effects of bariatric surgery on metabolism, describing the enhanced satiety that is achieved following surgery as 'I don't enjoy burgers any more' syndrome.

The small bowel can be seen as the 'pituitary of the gut', with levels of peptide-YY, glucagon-like peptide-1 and oxyntomodulin higher in response to feeding following the Roux-en-Y procedure. Furthermore, mice receiving transplants of gut microbiota from women who have undergone bariatric surgery do not gain weight on feeding. Restoration of activity of NKX6.1, a

potent bifunctional transcription regulator required for the development of β cells, may be one factor that leads to remission of type 2 diabetes. 'Reverse engineering' of the metabolic effects of bariatric surgery may not only help to understand and refine the traditional procedure, but could lead to the development of novel drug targets.

As well as invited lectures, members of the EGIR group gave short oral presentations based on submitted abstracts, several of which are published below.

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Conflicts of interest

There are no conflicts of interest.