Congress Interview

Francesco Giorgino, Senior Vice President of European Association for the Study of Diabetes (EASD), shared his insights from this year's congress. He discussed how a fascination with hormones led him to the field of endocrinology, his findings from insulin resistance research, and how EASD is contributing to diabetes research on a global scale.

Francesco Giorgino

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Citation: EMJ Diabet. 2024;12[1]:44-49. https://doi.org/10.33590/emjdiabet/OTLL4497.

Q1 What led you to pursue a career in endocrinology and diabetes?

I was fascinated by hormones from when I first learnt about hormones as molecules that can carry a signal from one tissue or cell to another; regulate cell growth, metabolism, and particularly some important functions or processes occurring in the body, like growth, sex development, and control of the important metabolites. I was fascinated by the concept that these molecules could find the receptor on the target cells, activate those receptors, and induce signals that the cell will be able to decipher and translate into a biological response. So, this concept was something that made me really attracted to endocrinology.

This is why I chose this specialty after completing medical school, and immediately I became very much acquainted with insulin receptors and insulin signalling. That became my very first research interest because, when I was a resident in the speciality school, I was already working in the lab on insulin receptor tyrosine kinase, and then this was the major topic for my post doctorate.

After I finished my residency, I spent a few years at the Joslin Diabetes Centre of the Harvard Medical School in Boston, Massachusetts, USA, looking at changes in insulin signalling in conditions of insulin resistance and diabetes. There was, I think, a fairly straightforward development of interests, starting from the concept of hormones as wonderful molecules regulating biological processes, and then deepening that in terms of research studying insulin action and signalling, and molecules involved in translating the biological message of insulin in target tissues such as skeletal muscle and fat.

Q2 Your research interests include the mechanisms of insulin resistance and β-cell dysfunction in Type 2 diabetes. Can you tell us more about your findings in this field?

Yes, as I mentioned, in my early research years I became very interested in and focused on insulin signalling changes in conditions of insulin resistance. So, in the

early 90s, about 30 years ago, there was a very important role attributed to insulin resistance as a pathogenetic factor leading to hyperglycaemia in Type 2 diabetes. It became more and more evident that β-cell dysfunction could be even more important than insulin resistance in promoting the development of hyperglycaemia in Type 2 diabetes.

My research was initially trying to understand how insulin action could be altered in insulin resistance, and then how β-cell secretory function could also be altered in conditions of obesity and Type 2 diabetes. This is my more recent focus, especially when I came back to Bari, where I established my own research group. We are focusing on the link between excess, dysfunctional adipose tissue and the development of β-cell dysfunction as a pathogenetic mechanism leading to hyperglycaemia in Type 2 diabetes.

We have characterised the role of some signalling proteins that are important in connecting adipose tissue dysfunction with β-cell dysfunction. One such protein is p66Shc, which is a redox sensor. It's a protein that can sense the excess of reactive oxygen species and, at the same time, can promote the generation of reactive oxygen species within the cells. We have shown that this happens in the β-cell, and it does happen in response to excess fatty acids. So, we believe that this protein can mediate the link between lipotoxicity and β-cell damage in obesity and in Type 2 diabetes. That's one piece of research that we have worked on quite a bit.

More recently, we have focused on some other molecules that could play not a detrimental role, but a positive one. One such protein is irisin. Again, this is also involved in the crosstalk between organs. For example, the skeletal muscle can release irisin when it is exposed to excess lipids, like in high-fat diets, or in response to exercise. So, there is a release of irisin from skeletal muscle in the circulation, and in this case, irisin is like a hormone that can improve the function and the survival of β-cells. We have published part of this research, and we also have ongoing studies showing that irisin can improve β-cell dysfunction in islets from people with Type 2 diabetes. This is something that is triggered by lipids, but eventually will positively affect the β-cell function.

Q3 What do you believe are some of the unique challenges associated with providing care for Type 1 and 2 diabetes? Are there any recent initiatives that the European Association for the Study of Diabetes (EASD) has implemented to overcome these challenges and advance patient care?

Yes, for sure, we are living in a very exciting time for both Type 1 and Type 2 diabetes therapeutic management. As we know, technology has become extremely important for the implementation of optimal glucose control in people with Type 1 diabetes. We have a variety of devices that can sense glucose changes and can also be integrated with the pumps that provide insulin

infusion to our patients, what we call the hybrid closed loop. Of course, we look forward to further developments of this concept in a fully automated closed-loop insulin delivery system.

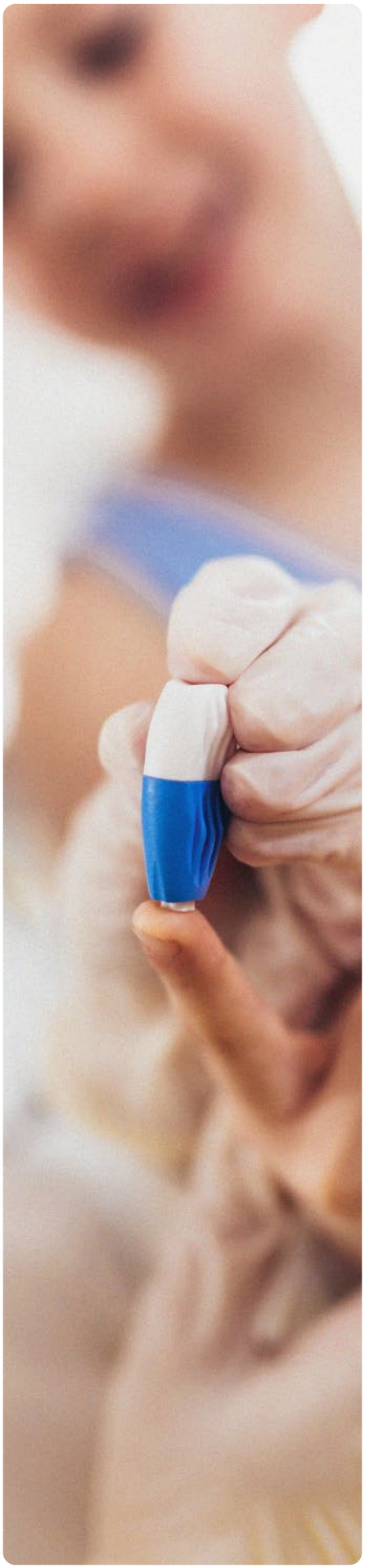
In this particular regard, I think the EASD has been progressively more active. We can appreciate that the EASD is very interested in promoting science exchange and knowledge in the field of automated insulin delivery. In the latest meeting we had in Madrid, Spain, we had a lot of sessions around diabetes technology in the congress, and also the participation of companies that promote and develop products in this particular field. So, we can say that at EASD we are welcoming more technology, and the presence of these technology companies may foster a scientific discussion about the different devices available and what they can provide to people with Type 1 diabetes.

At the same time, there's a very important, new, and interesting opportunity to delay the onset of Type 1 diabetes using the anti-CD3 monoclonal antibody teplizumab. Potentially, there may be other drugs that will be further characterised to interfere with, or potentially halt, the autoimmune aggression towards the β-cells in Type 1 diabetes. That's something that the EASD is looking forward to embracing and making people discuss at the Annual Meetings, as well as in dedicated courses, as the EASD also offers educational activities. A course focused on technology for Type 1 diabetes is under planning and will be available to any interested physicians.

Regarding Type 2 diabetes, we have to acknowledge how comprehensive the management for this form of diabetes has become. We can use drugs that not only target glucose levels and weight excess more efficiently than in the past, but also provide additional benefits to the heart, cardiovascular system, kidney, brain, and potentially even other benefits. I'm referring to the SGLT2 inhibitors, the GLP-1 receptor agonist, and the dual or triple agonist. So, again, that is something the EASD is very attentive to and has always provided a lot of room to discuss these new developments and new findings.

Q4 As EASD's Senior Vice President, what are your main objectives for the organisation, especially with tackling multimorbidity?

Well, of course, these objectives are defined by the EASD Board and the President of EASD, Chantal Mathieu, who is Professor of Medicine at the Katholieke Universiteit Leuven, Belgium. Within the Board, we have people who are engaged in specific activities. The honorary secretary, Tina Vilsbøll, Clinical Professor and Head of Clinic at Steno Diabetes Center, Copenhagen, Denmark, is the one who coordinates the scientific programme for the Annual Meeting. We have Julia Mader, Associate Professor of Medicine at the Division of Endocrinology and Diabetology at the Medical University of Graz and Deputy Head of the Diabetes Outpatient Clinic, Austria, who is in charge of postgraduate education. This includes all the activities that promote the education of physicians in the field of diabetes outside the Annual Meeting, mainly through the e-learning platform. EASD also offers an important programme for young investigators and young physicians called Early Career Academy, all of which is coordinated by Patrick Schrauwen,



Department of Nutrition and Movement Sciences, Maastricht University, The Netherlands.

The EASD has multiple projects and important activities, and I am now coordinating a new project focused on launching and implementing a Global Council that the EASD has just initiated. We had the first meeting of the Global Council in Madrid, chaired by me with Leszek Czupryniak of the Medical University of Warsaw, Poland, who is also our advisor on this project. This new initiative aims to embrace people, physicians, and researchers globally, given the global impact of the EASD and its activities, as evidenced by the fact that the Annual Meeting is attended by physicians from all over the world.

In fact, we noticed that the content we provide in the Annual Meeting, and the discussions we have, can attract physicians from all over Europe, as well as from countries outside Europe, like the Middle East, Asia, China, Japan, South America, North America, and Australia.

So, we now have the Global Council in which we have people that have been endorsed by national diabetes societies, and they represent different regions from all over the world. We have people from China, Japan, Africa, Australia, North America, Canada, the Middle East, Europe, Eastern Europe, Southern Europe, and Europe. The aim of this Global Council is to first make all the EASD initiatives better understood and known across the world so that people from any region or country can potentially apply to these initiatives and obtain benefits, and second, to collect feedback. Any input that can be conveyed to the EASD Board and can be considered for triggering new initiatives or new projects.

Q5 You chaired the 18th Albert Renold Lecture and 39th Camillo Golgi lecture at EASD 2024, two very prestigious sessions. What were the aims and key takeaways from this year's lectures?

The Albert Renold Prize has traditionally recognised excellent scientists in the field of islet biology and islet pathophysiology; from this year, the prize has been extended to acknowledge excellent research in various aspects of the pathophysiology of diabetes. This year, the committee has identified Lori Sussel, Professor at the University of Colorado Anschutz Medical Campus, Aurora, USA, as the recipient of this prize.

Sussel has developed extremely interesting studies and achieved very important accomplishments in the field of islet biology, particularly coupling the interest and expertise on transcriptional regulation to the understanding of the identity and functional properties of islet cells,

> **This will help us not only to understand and identify the mechanisms that link obesity with Type 2 diabetes**

and how this can be potentially lost in diabetes.
We know that it takes a very sophisticated mechanism for the β-cell to promote its function in releasing insulin, and also for other cells, like the alpha cells, to release glucagon. She has provided very important knowledge in understanding how this happens, what the role of specific transcriptional factors is, and also how this can be altered under conditions of diabetes. She also focused on post-transcriptional modifications, studying, for example, the long non-coding RNAs as another mechanism that can regulate islet function and the differentiation of β-cells. In her lecture, she described her earlier findings, went through the different contributions, and ended with the perspectives from her ongoing research.

Moving to the Camillo Golgi Prize, another very prestigious prize of the EASD, has always focused on the complications of diabetes. The EASD board has revisited the definition of this prize to be more modern to acknowledge not only excellent studies in the field of the classical complications of diabetes, but also the several comorbidities that associate with this disease.

This year, this prize was awarded to Rodica Pop-Busui, Associate Director for Clinical Research, Mentoring and Development; and Larry D. Soderquist, Professor in Diabetes, Professor of Internal Medicine Metabolism, Endocrinology, and Diabetes, and Vice Chair of Clinical Research Department of Internal Medicine, University of Michigan, USA. She is originally from Romania and received a fellowship in the 1990s, which led her to the University of Michigan, where she further advanced her career.

Pop-Busui has been always interested in the complications of diabetes. She has worked on neuropathy, both autonomic and somatic neuropathy. She has taken a more clinical and epidemiological approach compared to the previous awardee. Her lecture covered all the developments that were made in the field of neuropathy as a complication of Type 1 and Type 2 diabetes. I believe her key contribution has been to advance our understanding of diabetes complications by analysing significant studies, such as the DCCT study, along with other critical research that has focused on diabetes treatment. These studies have demonstrated the impact of both glucose control and specific medications in reducing the burden of diabetes-related complications.

Q6 You co-authored the abstract 'The real-world safety profile of tirzepatide: pharmacovigilance analysis of the FDA Adverse Events Reporting System (FAERS) database' presented at EASD 2024. What were your key findings from this study?

This is a study that was carried out by one of my coworkers, Irene Caruso, who is the lead author of this particular study, at the University of Bari Aldo Moro in Italy. She presented this paper at EASD as a short oral communication. This study stems from the interest in tirzepatide, which is a dual GLP-1 agonist that is currently approved and used for the treatment of both Type 1 and Type 2 diabetes and obesity in the USA and other countries. This drug is still not available in Italy, but we are expecting the drug that to change soon.

What we tried to understand is whether, by analysing the pharmacovigilance database of the FDA adverse events reporting system, we could replicate or get additional or diverse information about the tolerability and safety of tirzepatide as compared to other diabetes medications, particularly GLP-1 receptor agonists. The novelty of this analysis is that it is the first time that this database has been analysed in a rigorous and analytical way to get this information about tirzepatide. Furthermore, this drug was approved relatively recently, and it has only been available in the USA for the last 2–3 years.

We can get some interesting information because people use it and both physicians and patients report any adverse event that can occur during treatment in the FDA Adverse Events Reporting System (FAERS) database, which is fully accessible. Thus, this information can be analysed to get an idea about the tolerability and

the safety of tirzepatide versus other diabetes medications. We know that tirzepatide in the Phase III trials showed great efficacy on glucose lowering and weight loss, but was also associated with some side effects, particularly gastrointestinal side effects, and some signs of pancreatobiliary side effects that should also be taken into consideration.

In essence, our analysis shows that if you look at this real-world data, tirzepatide does increase the frequency of reporting of gastrointestinal adverse events and also, to some extent, reports of pancreatitis, diabetic retinopathy, or thyroid neoplasia, as it occurs in the Phase III trials, with some signal for gallbladder or biliary-related clinical events. So, in essence, this is the profile of tolerability and safety that we already know for tirzepatide and is not much different from the one of GLP-1 receptor agonists. Actually, there is probably, and this emerges from the analysis of the virus database, a similar, if not better, safety and tolerability profile of tirzepatide versus GLP-1 receptor agonists regarding the occurrence of these side effects, particularly if one considers the high efficacy of tirzepatide in promoting glucose reduction and weight loss. So, I would say overall, a reassuring outcome from our analysis.

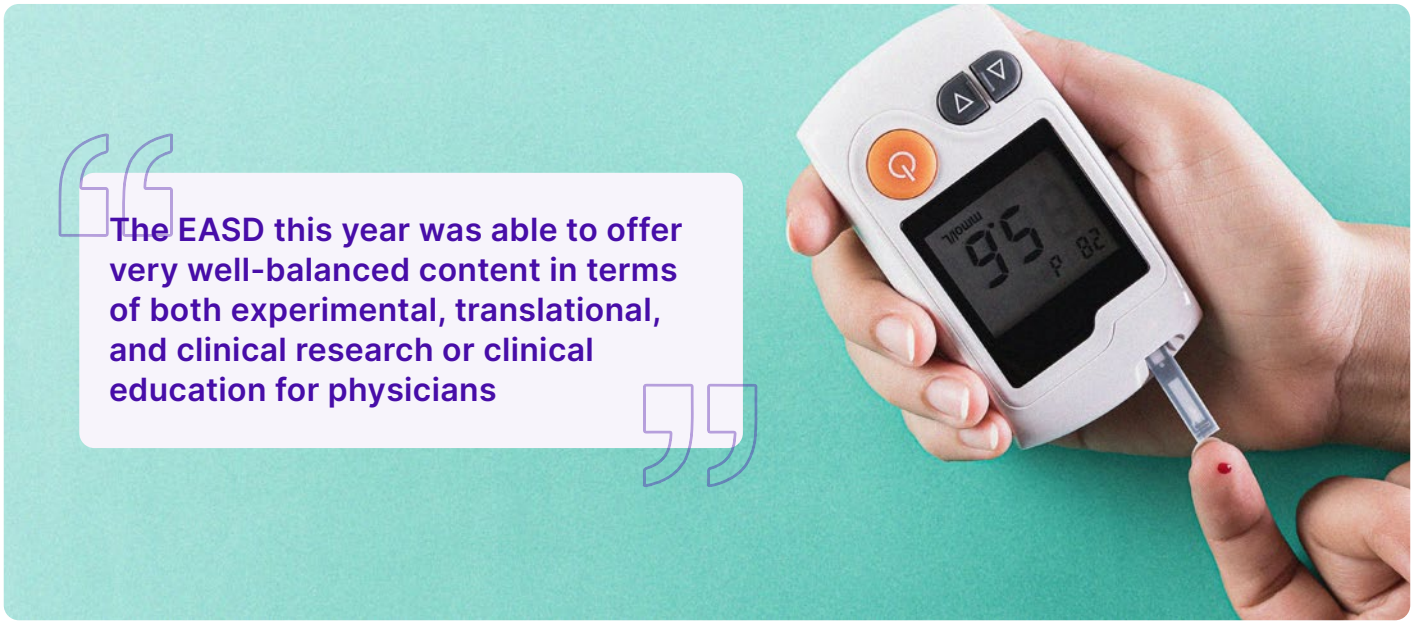
Q7 What would you say the highlights from EASD 2024 have been? How has the programme been different from last year?

Well, the programme was diverse and very rich. It focused on Type 1 and Type 2 diabetes and also had a lot of content around obesity, cardiovascular disease, and renal disease and education.
There were many sessions dedicated to technology in diabetes. The EASD this year was able to offer very well-balanced content in terms of both experimental, translational, and clinical research or clinical education for physicians, and I think this was the strength of the programme this year compared to the previous year.

This year, we had also very high attendance. The meeting was attended by more than 12,000 people in person in Madrid, and there were also about 1,500 who were following the meeting remotely. So, I think this is because of the wealth and diversity of the content that could be of interest to researchers, young researchers, clinical researchers, physicians, and in general, healthcare professionals working in the field of diabetes.

Q8 Where can we expect to see your research focus lie in the coming years?

The focus will be to further try and understand how the relationship between excess adipose tissue and dysfunctional adipose tissue and β-cell dysfunction develops. So, trying to further explore the crosstalk between these organs and also with other organs that could have an impact on β-cell function in a positive or negative way. Hopefully, this will help us not only to understand and identify the mechanisms that link obesity with Type 2 diabetes but also to potentially study some therapeutic targets that could help revert β-cell dysfunction that occurs in Type 2 diabetes. Irisin is one such example. We would like to further characterise the therapeutic value of irisin in Type 2 diabetes, but it is possible that additional molecules that are relevant to this particular goal could be identified. This is what we are currently trying to pursue in our research group.



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