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Q1 Your research has consistently focused on energy metabolism and insulin resistance. How has our understanding of energy metabolism in diabetes changed over the course of your career, and what do you think clinicians still underestimate about its importance?

Awareness of insulin resistance has been around for decades. It was already a major focus of research 20 years ago, or even earlier, and was considered one of the most important features of obesity and Type 2 diabetes (T2D). Later, particularly over the last few years, there was a general feeling in the field that we already knew everything about insulin resistance, and it became less fashionable to research.

> **This gap in routine measurement is exactly what limits how much value energy metabolism research currently delivers at the bedside**



Surprisingly, at last year's annual meeting of the European Association for the Study of Diabetes (EASD), some colleagues and I were invited to write a consensus paper on insulin resistance and its novel developments, summarising what has changed and what we have learned over the last decade or so.

Three things stand out. The first is the molecular mechanisms of insulin resistance. The second is the tissue-specific differences in how it presents. The third is the discovery of novel organs or tissues that had not previously been associated with insulin resistance, such as the brain. So, it turns out that insulin resistance is coming back as an important feature in understanding metabolic disease.

It's a little different for energy metabolism, which has always been somewhat fuzzy in terms of clinicians' understanding. Different groups have carried out different kinds of research over the years, but clinicians as a whole are generally not familiar with the detailed knowledge behind energy metabolism, simply because it is mostly not measured in clinical practice. That, I think, is the real limitation: clinicians usually don't measure insulin resistance, even though it's fairly straightforward to do, and this gap in routine measurement is exactly what limits how much value energy metabolism research currently delivers at the bedside.

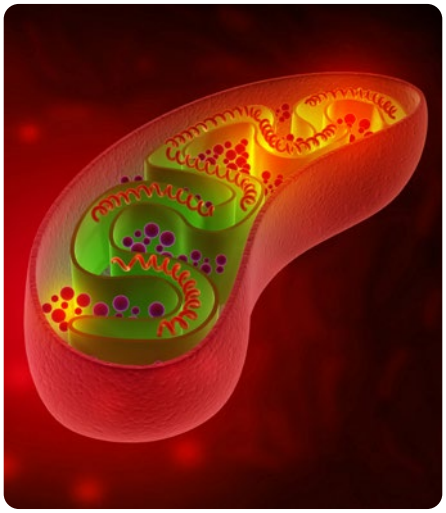
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Q2 Another notable portion of your work revolves around mitochondrial dysfunction, which is often discussed as an important feature of insulin resistance and metabolic disease. What do we now understand about the specific role mitochondria play in the development of diabetes, and, importantly, is mitochondrial dysfunction a cause of diabetes, a consequence, or both?

This follows on from energy metabolism, since measuring mitochondrial function is key to understanding it. You can measure whole-body energy metabolism in humans using indirect calorimetry, but the real thing is to measure the functionality of the organelles within cells actually responsible for it, the mitochondria.

I don't really like the term 'mitochondrial dysfunction', because mitochondrial functionality has several distinct aspects: a sufficient number of mitochondria, mitochondria that are functioning properly, an intact network of them within the cell, and the individual components, some synthesised by the nucleus and others by the mitochondria themselves. There isn't one simple 'mitochondrial dysfunction'; several aspects can be abnormal independently.

It's only in the last 10 years that we became able to directly assess mitochondrial function in the human liver, using biopsies from patients with obesity undergoing bariatric surgery and a micro-method we developed to measure oxygen consumption and function. That's still relatively new work, done by only a handful of groups worldwide. It's much better established for skeletal muscle, but almost unknown for adipose tissue.



What we've found is that different organs respond differently to metabolic challenges. If you infuse a lot of lipids, which causes insulin resistance, skeletal muscle mitochondria reduce their function, whereas the liver upregulates its oxidative capacity during a lipid challenge or the development of obesity. It handles the excess energy but at the cost of oxidative and endoplasmic reticulum stress. In the long run, this can favour MASLD, steatohepatitis, and eventually fibrosis and cirrhosis.

So, is mitochondrial dysfunction a cause or a consequence of diabetes? Both are correct. There are inherited forms of diabetes in which people, even if lean, show abnormalities in their skeletal muscle mitochondria. One specific example is maternally inherited diabetes, a genetic defect transmitted from mother to child when the mother donates her mitochondria to the next generation. If those mitochondria are abnormal, this can affect the brain, muscle, and particularly the β cells, since the brain and β cells have high energy demands.

The β cell is like a perfect computer monitoring small changes in glucose and responding with insulin secretion, mediated by mitochondrial function. If this fails, people develop diabetes. That's 'mitochondrial dysfunction' as a cause, but long-term exposure to lipids and high energy intake can also change mitochondrial function over time, as with the liver example above. Mitochondria are also involved in diabetic neuropathy, since nerves, like the brain, require intact mitochondrial function.

In summary, it's both a cause of diabetes and obesity, and also part of the disease process in diabetes and its complications.

Q3 We have traditionally thought about obesity and diabetes largely in terms of how much adipose tissue someone has. Your work has helped contribute to a more nuanced understanding of where fat is stored and how it behaves metabolically. How important is it to move from thinking about the amount of adiposity to thinking about the quality and distribution of adipose tissue, and what role does this play in conditions such as insulin resistance, T2D, and fatty liver disease?

I think obesity is the key disease here, since in many cases it's the precursor of both T2D and MASLD. What we've found is that it's not only the amount of energy stored in adipose tissue that matters, but particularly how the adipose tissue handles the energy coming in.

It's the visceral adipose tissue that appears to be responsible. Abdominal obesity, with fat stored viscerally, is well known to be tightly associated with diabetes, complications, and cardiovascular disease. Coming back to the studies we did in bariatric surgery patients, we

> **Even though the visceral depot is much smaller than the subcutaneous depot, it's as important as an endocrine organ**

also took adipose tissue biopsies from different depots, visceral and subcutaneous. It turns out that, early in the development of obesity and MASLD, it's particularly the visceral adipose tissue that becomes insulin resistant and develops a reduction in mitochondrial functionality, associated with early adipose tissue inflammation.

The concept, also known from preclinical studies, is that this inflamed, abnormal visceral adipose tissue sends signals, first to the liver but also to other tissues, through adipokines: adiponectin, the 'good guy', and inflammatory markers such as IL-6 and TNF-α, the 'bad guys'.



So, even though the visceral depot is much smaller than the subcutaneous depot, it's as important as an endocrine organ, and is one of the earliest abnormalities we find during the development of obesity.

Q4 There is increasing recognition that sex influences metabolic disease, from fat distribution and insulin sensitivity to the way diabetes and its complications develop and progress. Do you think we have adequately incorporated biological sex into diabetes research and clinical practice, and what are the most important differences clinicians should be paying attention to?

The easy answer is that, despite decades of accumulating evidence, we still don't adequately acknowledge sex differences in metabolic outcomes.

Over roughly the last 15 years, most journals have required studies to include equal numbers of males and females, and now different ethnicities too, so that sex differences can be properly analysed. That wasn't the case before. Most historical studies were done in young, healthy males, or young males with diabetes, so the amount of data is still not perfect, though it continues to grow.

As you mentioned, differences in adipose tissue distribution matter for metabolic outcomes. What's also important is how males and females cope differently once they have diabetes or obesity. We looked at psychological and health-related features in our cohort, and there are substantial differences between males and females, and between the different subtypes of diabetes, in how people deal with the disease. Females tend to lean more towards depressive symptoms, whereas males often don't take the disease and its complications as seriously, and that translates into differences in how complications develop.

This is particularly true for diabetes-related cardiovascular disease. It has long been known that females don't present with the typical symptoms of myocardial infarction that males do, so a heart attack in a woman is often not recognised early and, as a result, not adequately treated.

There are also sex-specific forms of diabetes: gestational diabetes and polyendocrine metabolic ovarian syndrome, a phenotype that is insulin resistant, shows an unhealthy pattern of fat distribution, and involves abnormalities in sex hormones, including higher testosterone. The same holds for males: when testosterone secretion declines, there can also be changes in adipose tissue distribution that make them more prone to insulin resistance. So, we know a good deal, but there's considerable learning still to do.

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Q5 Ethnic differences in diabetes risk are also well recognised. From a metabolic perspective, what do you think underlies these differences in diabetes susceptibility between populations, and how close are we to replacing broader ethnic risk categories with more biologically meaningful measures?

It's well known that certain groups have a markedly elevated genetic risk of diabetes. Pima Indian people in Arizona, USA, for example, become obese and develop diabetes and its complications very early in life. That's been known for decades. There are also long-recognised differences in risk among other populations. In India specifically, there's a different pattern of adipose tissue distribution. People from India are considered obese at lower BMI thresholds than people from Europe, largely because they tend to have a greater ratio of visceral to subcutaneous adipose tissue, which is considered one of their pathogenic features. They also tend to have lower insulin secretion.

Precision medicine approaches are now being applied to different populations worldwide, and it turns out that the diabetes subtypes in India differ from those in Europe or the USA, with a much higher proportion of severe, insulin-deficient diabetes, independent of the different adipose tissue distribution. So, it's increasingly recognised that there are real differences in pathogenesis between populations and this does matter for treatment.

Newer drugs are emerging to get around existing issues with drugs like insulin sensitisers, which cause adipose tissue to store fat more effectively, so patients gain weight even as their metabolism improves, which isn't ideal in the long run. Insulin sensitisers are still used more in places like India, where adipose tissue function plays a bigger pathogenic role. In Japan and East Asia, by contrast, there's a more specific defect in insulin secretion, and patients respond to treatments that don't work in patients from Europe: imeglimin, for instance, acts on the β cells and works well in Japan, where it's approved, but it isn't approved in Europe, because it simply doesn't work there.

Finally, there's a newly proposed diabetes type, specific to some Asian and African cohorts, in which lean people who are not overeating, but rather undernourished, develop diabetes in a distinct way. Whether this represents a specific genotype or phenotype is still an open question, but it was proposed at the last International Diabetes Federation meeting in Bangkok, Thailand.

> **There may well be treatments that specifically address particular subtypes, targeting insulin secretion or specific complications**



Q6 If we put these pieces together: energy metabolism, mitochondrial function, adipose tissue distribution and composition, and differences related to sex and ethnicity, it becomes increasingly difficult to think of T2D as a single disease. How close are we to using this biological information to genuinely personalise diabetes prevention and treatment, rather than simply describing different subtypes?

We introduced the term 'precision diabetology' a few years ago, building on our own work and initiatives from Sweden, and validated the concept in our German Diabetes Study cohort. We found four sub-phenotypes of T2D, differing in insulin secretion, insulin sensitivity, obesity, and age, which are the leading features.

It turns out you only need age, sex, glucose control, insulin secretion, and insulin sensitivity to separate these groups.

That finding has now been repeated all over the world. Other groups have since shown there are distinct genotypes too. If you combine the genes associated with diabetes, you can also arrive at six or eight subtypes, which look fairly similar to the phenotype-based ones. Moreover, you can find the same pattern in pre-diabetes. That makes the point that there are inherited, or very early, metabolic changes that differ between groups and that ultimately end up as different subtypes of diabetes.

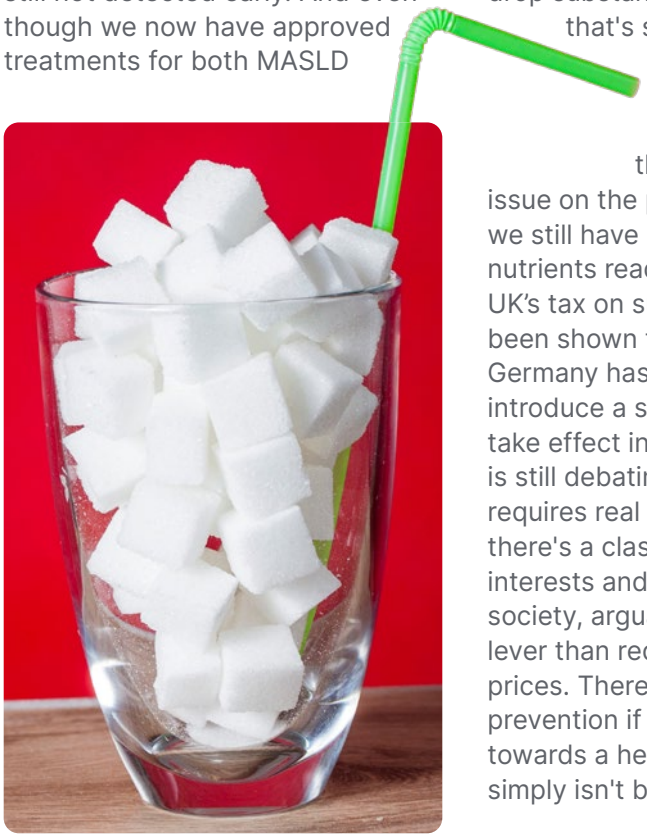
Does this have clinical impact? At the moment, the most important impact is that these subtypes differ in how complications develop. The mildly obese and age-related subtypes tend to be relatively benign and don't rapidly develop complications, whereas the severe insulin-resistant subtype presents early with abnormal kidney function, a higher risk of MASLD, and an earlier, higher risk of cardiovascular complications. The insulin-deficient phenotype, meanwhile, tends to develop neuropathy and retinopathy, which relate to higher glucose levels.

If you ask whether we have firm conclusions about differences in treatment response, that's less clear at the moment. Retrospective studies suggest that knowing a patient's subtype might help guide treatment, but there are currently only one or two RCTs looking into this, and they don't really confirm that yet. In the future, there may well be treatments that specifically address particular subtypes, targeting insulin secretion or specific complications, but it's not something we have the capacity to do yet.

Q7 You have spent much of your career working at the interface between fundamental metabolic research and clinical medicine, and you have also been involved in shaping diabetes research and guidelines at a national and European level. Where is the biggest disconnect today between what metabolic research tells us and what clinicians are actually able to do for their patients? What needs to change at a policy level if we are to bridge that gap?

Although there are many questions still to address, and we don't know everything about diabetes and its complications, we already know enough to markedly improve early diagnosis and to prevent complications. It's still not being done perfectly, simply because that requires strategic policy developments in different countries.

Take MASLD, which for a long time wasn't acknowledged as a complication or risk of diabetes. Awareness is still an issue, as many people don't realise the liver can be affected by diabetes. We need to raise that awareness, which isn't trivial. Secondly, treating diabetes-related liver disease requires a multidisciplinary approach involving hepatologists, diabetologists, dieticians, and others, and that isn't in place everywhere; there are models of care in various regions that work extremely well, but usually only on a small scale. As a result, the role of MASLD as a cause of cirrhosis has been rising over the last decade, and it's often still not detected early. And even though we now have approved treatments for both MASLD and diabetes and obesity, they are often expensive, not reimbursed by insurers, or otherwise inaccessible to patients.



It starts with awareness, which needs not just doctors, but the healthcare system and politicians, moves through the interaction between disciplines, and ends with reimbursement and financing of integrated care. There's a lot of ongoing discussion about whether we need a dedicated model of care for obesity, what it would cost, and whether it's worth the money. The same applies to certain complications: it's better established for heart and kidney disease, but far less so for the liver and for neuropathy. That's the main reason there's still a gap between what we know and what gets translated into everyday clinical practice.

The next real shift will come once these newer incretin drugs and co-agonists lose their patents, at which point prices will most likely drop substantially, but, for now, that's still some way off.

Beyond awareness and drug treatment, there's also a major issue on the prevention side, since we still have a lot of unhealthy nutrients readily available. The UK's tax on sugary drinks has been shown to be effective, and Germany has already decided to introduce a similar tax, expected to take effect in 2027, while Austria is still debating the idea. This requires real policy action, and there's a clash between industry interests and the interests of society, arguably an even bigger lever than reducing medication prices. There's huge potential in prevention if we can move people towards a healthier lifestyle, but it simply isn't being done.

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Q8 Looking ahead, what questions are you and your team most excited about now? After such extensive work on insulin resistance, energy metabolism, mitochondria, and metabolic heterogeneity, what do you think is the next major piece of the puzzle, and which discovery would have the greatest impact on diabetes care over the next decade?

There are different levels to this. One is that we still need to better understand the disease itself, both Type 1 and T2D. Precision diabetology is still very much at the beginning rather than the end. That means not only understanding the different subtypes better, but integrating multi-omics data, proteomic and transcriptomic information, to eventually arrive at a set of variables or scores that allow something close to truly individualised treatment in the long term. That remains one of our most important research questions at the institute.

Beyond that, we're interested not just in the role of nutrition and genetics, but in the role of the environment, particularly climate. We've looked at air pollution as one cause of diabetes, and we're now interested in how climate change and shifting temperatures might affect the disease, which isn't well understood at the moment. We know that very low temperatures actually improve metabolism, because they regenerate brown fat, which isn't normally present in adult humans. For example, people who regularly expose themselves to cold water, whether through ice baths or cold-water swimming, can end up with more brown fat and improved metabolism. However, that is data derived from clinical studies and cannot be recommended to everyone as a treatment. The open question is what happens at the other extreme, with high temperatures. Some early studies suggest negative effects, others suggest none at all, but this needs to be understood, because it will become an increasingly important issue.

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What's missing is this: we now know how to help people lose weight very effectively with drugs, but we still can't properly address diabetes-specific complications. Neuropathy is the biggest gap; treatment there is still almost medieval, in that we only manage symptoms and have no effective causal therapy. For liver disease, we now have one or two approved drugs, but that's also still early, since 30–40% of patients don't respond. Complication-specific treatment remains a wide-open issue, and understanding novel approaches that work independently of the incretins' weight-loss effect, mitochondria-active drugs among them, is something everyone in the field is very interested in.