HEALTHCARE GROUP

CENTRE FOR DIABETES & ENDOCRINOLOGY

CDE Academy - Diabetes Literature Review

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Academy

UKPDS Legacy Effects: The Importance of Treating Hyperglycaemia Early

I'm pleased to give an update on the UK Prospective Diabetes Study (UKPDS). This is the longest-running follow-up of a randomised controlled trial in type 2 diabetes. Those familiar with it may remember that the 20-year trial randomised patients to intensive blood glucose control with sulfonylurea/insulin, or in overweight patients, to metformin, compared with a conventional (primarily diet) policy. The end of that trial showed unequivocally that better glucose control could reduce complications — that is, microvascular complications — but did not impact macrovascular complications.

Once the trial finished, we embarked on a 10-year post-trial monitoring study in which all patients who had survived continue to be followed by the UKPDS team. The results from the end of that 10-year period showed that not only was the microvascular protection maintained, but we saw emerging risk reductions both for myocardial infarction and for all-cause mortality. This emerging risk and continued risk protection, we term the "legacy effect" — that is, a continuing benefit from early intensive glucose control.

Today, I want to bring you new results because we have a further 14 years of data to add. In this third phase of the UKPDS, we have engaged with the NHS (National Health Service), which is countrywide in the UK and free at the point of delivery. This allows us to collect administrative data - that is, hospital episode statistics and death registry data.

By combining this with the clinical trial data and the post-trial monitoring, we have been able to extend the follow-up to 44 years. We have asked the same questions again: If you treat early and intensively with sulfonylurea or insulin, do you see continuing benefit? The answer is, unequivocally, yes. We see 11% fewer deaths and 25% fewer microvascular events - that's kidney disease and loss of vision, which are the things which scare our patients so much. This is a legacy effect which appears to be enduring, and I'll come back to that.

We also have the trial comparing metformin. In the metformin trial in overweight patients, the legacy effect for metformin also continues. We see a 31% reduction in heart attacks and a 25% reduction in all-cause mortality. That's a one-quarter reduction. These are amazing figures with absolutely stable legacy effects. The question that we have to address is, why is this continuing benefit seen? My view is that what we are looking at is a hyperglycaemic legacy effect. I believe that early hyperglycaemia really does set the pattern for the rest of a patient's life. We're seeing irreversible pathophysiologic changes occurring either through oxidative reactions, inflammatory promotion of the pathways, or epigenetic changes, which seem to set people on a permanent path to be at increased risk.

Improving their control at a later time certainly reduces their risk, but it never gets them back to the minimal risk that's possible if you treat early and treat well.

I think there are big clinical messages here. Metformin clearly has an advantage. It's now used in non-overweight patients as well as overweight patients. It's extremely inexpensive, and our health economic analyses show that it is not only cost-effective, it's cost-saving.

The health economic analyses that we've conducted in parallel also show that these intensive therapies extend life with sulphonylureas or insulin, in the order of a year extra and with metformin, 2.7 years extra. That might not seem much, but in terms of clinical trial data, this is almost identical to what is seen with a lifetime simulation for the heart protection study with simvastatin, where they saw extensions of life between 1 and 2 years.

I think we have a clear message: If you identify and treat people with type 2 diabetes early and if you can avoid hyperglycaemia, you can avoid putting them on a high-risk trajectory for complications. This doesn't preclude the use of other drugs. We're not saying that metformin and/or sulphonylureas are necessarily first-line drugs, but they are up there with the other drugs as potential complementary agents, certainly in people who don't yet have complications. I think it's cementing their place for many years into the future.

Holman RR, Harmel M. UKPDS Legacy Effects: The Importance of Treating Hyperglycemia Early. *Medscape*. September 27, 2022.

Targeting Insulin Resistance Instead of Hyperglycemia in Type 2 Diabetes

Strasbourg, France - An international team coordinated by researcher Vincent Marion, PhD, deputy director of the French National Institute of Health and Medical Research (Inserm)/University of Strasbourg Medical Genetics Laboratory, has published the results of its research on a molecule called PATAS in the journal Diabetes. This drug could herald a new therapeutic era in type 2 diabetes. Medscape Medical News interviewed Marion about this molecule.

Medscape Medical News: Available antidiabetic treatments mitigate the consequences of type 2 diabetes by focusing primarily on glycemic regulation. In contrast, your new approach targets the underlying biologic mechanism responsible for the disease. What does it involve?

Marion: Our study, conducted in collaboration with the University of Birmingham in the United Kingdom, Monash University in Australia, and Dr Alexander Fleming, former director of the Diabetes Division of the US Food and Drug Agency, shows that our peptide drug called PATAS - an acronym for "peptide derived from PKC alpha targeting ALMS" - treats the actual source of diabetes. The first representative of a novel class of antidiabetic drugs christened "adipeutics," as a result of their specific targeting of the adipocyte; its distinctive feature is that it treats insulin resistance. In mouse, rat, and dog models, our new therapy specifically restores glucose absorption in the dysfunctional adipocyte.

"Using PATAS in the form of once-weekly subcutaneous injections in abdominal fat in diabetic mouse models, adipocytes that no longer had access to glucose were once again able to absorb it and then metabolise it to synthesise and secrete beneficial lipids throughout the body"

Medscape Medical News: So are you re-establishing insulin signalling in the dysfunctional adipocyte to treat insulin resistance?

Marion: In fact, PATAS specifically targets adipocytes by restoring glucose absorption in those cells, thereby re-establishing the metabolic physiology of adipose tissue. Fat cells control insulin resistance by absorbing 10% of circulating glucose. This fuels a process that is very beneficial in the case of adipose tissue, namely lipogenesis. Therefore, we are not targeting an indication with antihyperglycemic treatment, but rather with "insulin-resistance treatment," because this mechanism represents the root of the problem in type 2 diabetes, in hepatic steatosis and fibrosis, and in associated cardiovascular diseases. Improving the physiology of adipose tissue restores lipid homeostasis. Until now, adipose tissue has been overlooked or even ignored in diabetes treatment research on the pretext that it absorbs only a small amount of circulating glucose.

Medscape Medical News: How did you devise this research strategy?

Marion: This study arose out of previous work conducted by our team, which had identified a new therapeutic target against type 2 diabetes by focusing on an ultrarare monogenic illness, Alström syndrome. We showed that adipose tissue abnormalities caused by the loss of function of the ALMS1 protein induce extremely severe insulin resistance associated with early-onset type 2 diabetes in individuals with this syndrome. We confirmed in animals that restoring the function of this protein in adipocytes alone re-established glycaemic balance. We then took a closer look at ALMS1 and how it interacts with other proteins in adipocytes. In the absence of insulin, it binds to another protein called PKC alpha. Conversely, activation of insulin in the adipocyte causes these two proteins to separate, resulting in glucose absorption. In patients with type 2 diabetes, who are consequently insulin-resistant, this bond between the two proteins is maintained. Our idea was, logically, to design a peptide (i.e., PATAS) that breaks the interaction between ALMS1 and PKC alpha, with a view to re-establishing insulin signalling in the dysfunctional adipocyte.

Medscape Medical News: What were your results?

Marion: Using PATAS in the form of once-weekly subcutaneous injections in abdominal fat in diabetic mouse models, adipocytes that no longer had access to glucose were once again able to absorb it and then metabolise it to synthesise and secrete beneficial lipids throughout the body, while at the same time absorbing extremely toxic lipids - non-esterified fatty acids. The effects can be seen in animals, with a marked improvement in insulin resistance, as evidenced by a dose-effect reduction in the homeostatic model assessment index by a factor of five after 1 month of treatment, and in other parameters and comorbidities, particularly improved glycaemic regulation. In fact, the glucose tolerance test improved significantly in diabetic animal models. In addition, liver steatosis and fibrosis were considerably reduced in all diabetic animal models tested, including in one of the reference models for fatty liver disease, namely the Japanese STAM mouse model. Thus, PATAS reduced hepatic steatosis by 60% and hepatic fibrosis by 40% after only one month of treatment at a dosage of 2 mg/kg/week.

Medscape Medical News: When does the next step begin?

Marion: A phase 1 clinical trial to test this new therapeutic pathway is planned in 2023. To date, we are the first team to develop this mechanism of action - treating diabetes by restoring the physiology of adipose tissue - using an antidiabetic agent that also seems to be better tolerated by patients. However, the data are still confidential. This invention is already protected by several patent families.

Targeting Insulin Resistance Instead of Hyperglycemia in Type 2 Diabetes. ***Medscape.*** **August 09, 2022.**

EASD 2022 - Diabetes drug tirzepatide shows striking results in overweight/obese adults

Takeaway

A once-weekly dose of tirzepatide 5 mg, 10 mg, or 15 mg demonstrated substantial and sustained body weight reduction in adults who were overweight or obese and did not have diabetes.

Tirzepatide also improved several prespecified cardiometabolic risk factors and the quality of life (QoL).

Gastrointestinal events of mostly mild/moderate intensity were the most frequently reported adverse events.

The World Health Organization defines obesity as 'excess or abnormal adipose tissue that causes a deterioration in health,' and clinicians have finally started to acknowledge it as a metabolic disorder.

Although in the past, lifestyle changes were mostly employed to control obesity, various clinical guidelines now advocate the use of anti-obesity drugs for those who are overweight or obese. Recent studies have shown that glucagon-like peptide-1 (GLP-1) receptor agonists and glucose-dependent insulinotropic polypeptide (GIP) receptor agonists can play a role in regulating food intake and aiding weight loss.

Tirzepatide, which has been approved by the Food and Drug Administration for type 2 diabetes, can bind to both the GIP and GLP-1 receptors and may, therefore, induce weight reduction.

The multicentre, phase 3 SURMOUNT-1 study was designed to evaluate the efficacy and safety of tirzepatide in people with obesity or overweight who did not have diabetes.

The trial included 2539 adults with a body mass index of ≥30 kg/m^2 or ≥27 kg/m^2 and with at least one weight-related complication.

Participants were randomly assigned to receive once-weekly subcutaneous tirzepatide (5 mg, 10 mg, or 15 mg) or placebo for 72 weeks.

The primary objectives of the SURMOUNT-1 study were to compare the effectiveness of tirzepatide 10 mg or 15 mg versus placebo at week 72 in terms of percentage change in body weight and percentage of participants with ≥5% body weight reduction.

Some of the key secondary endpoints focused on demonstrating the superiority of the drug over placebo in improving systolic blood pressure, fasting insulin and lipid levels, and the physical function score on the 36-item Short Form Health Survey (SF-36).

At week 72, the mean change in weight reduction was higher with all three doses of tirzepatide (15 mg: −22.5%; 10 mg: −21.4%; 5 mg: −16.0%) versus placebo (−2.4%).

Furthermore, a higher proportion of participants achieved body weight reduction of ≥5% with tirzepatide 15 mg (96.3%), 10 mg (96.2%), and 5 mg (89.4%) versus placebo (27.9%).

This drug also improved the overall body composition by reducing the ratio of total fat mass to total lean mass from 0.93 at baseline to 0.70 at week 72. Apart from weight reduction, tirzepatide improved systolic and diastolic blood pressures, fasting insulin levels (~47%), and triglyceride levels (>27%).

Among participants with prediabetes, >95% reverted to normoglycaemia after receiving the drug for 72 weeks. Additionally, there was an improvement in all domains of health-related QoL, and the SF-36 physical function score increased by 3.6 units with tirzepatide versus 1.7 units with placebo.

Gastrointestinal events of mostly mild/moderate intensity were reported in the treatment arm, and <5% of participants discontinued the study due to gastrointestinal events.

With all the evidence in favour of tirzepatide, Dr Jastreboff concluded by quoting one of the trial participants who said, "It's just as easy to lose weight as it ever was to gain weight."

"This drug also improved the overall body composition by reducing the ratio of total fat mass to total lean mass from 0.93 at baseline to 0.70 at week 72."

Reported on Univadis.com. The study was funded by the American Diabetes Association, Eli Lilly, and other sources.

Jastreboff AM, Aronne LJ, Ahmad NN, et al.; SURMOUNT-1 Investigators. Tirzepatide Once Weekly for the Treatment of Obesity. *N Engl J Med*. 2022 Jul 21;387(3):205-216. doi: 10.1056/NEJMoa2206038. Epub 2022 Jun 4. PMID: 35658024.

HbA1c-based screening shortens time to diagnosis of type 2 diabetes

Takeaway

HbA1c-based screening for undiagnosed diabetes can shorten the time to diagnosis of type 2 diabetes in middle-aged adults.

Why this matters

Type 2 diabetes is often asymptomatic and may be present long before clinical diagnosis. Previous studies have not directly measured the extent to which HbA1c-based screening cuts the time to diagnosis.

Study design

Study population was 179,923 UK Biobank participants aged 40 - 70 years with HbA1c measured and data linked to primary and secondary health care.

Undiagnosed diabetes was defined as a UK Biobank-measured HbA1c ≥48 mmol/mol (≥6.5%).

Funding: Research England, National Institute of Health Research, Wellcome Trust.

Key results

Of 166,846 participants without a pre-existing diabetes diagnosis, 1.0% (95% CI, 1.0%-1.1%) met criteria for undiagnosed diabetes with median HbA1c 51.3 mmol/mol (6.8%).

The 1703 participants with undiagnosed diabetes represent an extra 13.0% (95% CI, 12.4%-13.6%) with diabetes in the study population in addition to the 13,077 participants with known diabetes.

"Previous studies have not directly measured the extent to which HbA1c-based screening cuts the time to diagnosis"

Over median 7.3 years, 87.7% (95% CI, 86.1%-89.2%) of the 1703 participants who met undiagnosed diabetes criteria at enrolment subsequently received a clinical diagnosis of diabetes at a median time 2.2 (95% CI, 2.0-2.4) years.

Median HbA1c at diagnosis for the 76.3% (n=1300) with an at-diagnosis HbA1c value recorded in primary care was 58.2 mmol/mol (7.5%).

For those with undiagnosed diabetes at enrolment, male vs female sex and enrolment BMI ≥30 kg/m^2 (vs lower) were associated with shorter time to diabetes diagnosis (HRs, 1.12 [95% CI, 1.00-1.25] and 1.25 [95% CI, 1.12-1.39], respectively).

Higher enrolment HbA1c was also strongly associated with shorter time to diagnosis (compared with 48.0-52.9 mmol/mol: HRs, 2.13 [95% CI, 1.84-2.46] and 2.71 [95% CI, 2.37-3.09] for 53.0-57.9 mmol/mol and ≥58.0 mmol/mol, respectively).

Limitations

UK Biobank participants tend to be healthier, more often of White ethnicity, and have better outcomes than the general UK population, and thus the actual proportion with undiagnosed diabetes is likely higher.

Insufficient follow-up time to determine the effect of screening on complication rates.

Young KG, McGovern AP, Barroso I, Hattersley AT, Jones AG, Shields BM, Thomas NJ, Dennis JM. The impact of population-level HbA1c screening on reducing diabetes diagnostic delay in middle-aged adults: a UK Biobank analysis. *Diabetologia.* 2022 Nov 22 [Epub ahead of print]. doi: 10.1007/s00125-022-05824-0. PMID: 36411396