HEALTHCARE GROUP

CENTRE FOR DIABETES & ENDOCRINOLOGY

CDE Academy - Diabetes Literature Review

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Gut Microbiome Linked With Incident Type 2 Diabetes

Key Takeaways

Four species from the *Lachnospiraceae* family of bacteria that are common in the gut microbiome among healthy Finnish adults were associated with incident type 2 diabetes during long-term follow-up.

Researchers found the association in two geographically and genetically separate regions of Finland. This unprecedented finding requires validation in different cohorts.

Study Design

Analysis was perfromed on 5572 residents of Finland enrolled in the FINRISK study in 2002 when they were 24-74 years old. All participants had a stool specimen collected at enrolment that was subsequently analysed for its microbiome content.

Researchers tracked incident type 2 diabetes during a median follow-up of 15.8 years.

Key Results

During follow-up, 432 people (8%) developed incident type 2 diabetes.

Out of 119 different taxa identified in the specimens, 15 had positive associations with incident type 2 diabetes and three had negative associations in analyses that adjusted for several known risk factors.

Most of the positively associated taxa were from the family *Lachnospiraceae*, with several from the genus *Clostridium*. Two of the three negatively associated taxa were from the genus *Alistipes*.

Overall, the investigators identified four species from the family *Lachnospiraceae* that showed robust association with a higher type 2 diabetes risk in two geographically and genetically separate regions of Finland.

All four of the diabetes-associated taxa have been previously linked with other metabolic diseases and risk factors, such as obesity and fatty liver disease.

Limitations

The study used a technique known as 'shallow shotgun metagenomics' to analyze the microbiome contents, which limits the study to describing associations between taxa and incident disease. This depth of genetic sequencing precludes more comprehensive and detailed genomic assessments.

Disclosures

The study was primarily supported by grants from several noncommercial organizations in Finland.

A collaborating US microbiome research center received funding from Illumina and Janssen.

One author has received honoraria from Servier, and another has received an honorarium from Sanofi and research support from Bayer.

Gut Microbiome Linked With Incident Type 2 Diabetes. *Medscape*, 29 November, 2021.

NICE Updates Recommendation on the Management of Diabetes

NICE has issued updated guidance on the *management of type 2 diabetes (T2D) in adults.* This includes new recommendations on the treatment of T2D in *people with chronic kidney disease (CKD)*. The 2021 recommendations advise that people with CKD and T2D and an albumin-to-creatinine ratio (ACR) of 3 mg/mmol or more should be offered an angiotensin receptor blocker (ARB) or an angiotensin converting enzyme (ACE) inhibitor, titrated to the highest licensed and tolerated dose.

For people with CKD who are already receiving an ARB or an ACE inhibitor at the highest tolerated dose, an SGLT2 inhibitor should be offered in addition to the ARB or ACE inhibitor if their ACR is at least 30 mg/mmol and they meet the prescribing criteria, including eGFR thresholds. NICE also advises that SGLT2 inhibitors can be considered for people with an ACR of between 3 and 30 mg/mmol; however these drugs may not be suitable for all people in this group.

The recommendations follow the publication of strong evidence from randomised controlled trials which showed that SGLT2 inhibitors reduced the risk of CKD progression, mortality and cardiovascular events in adults with T2D. Economic modelling found that SGLT2 inhibitors were likely to be both more effective and cost saving than standard treatment for people with an ACR above 30 mg/mmol.

"The 2021 recommendations advise that patients with CKD and T2D and an albumin-to-creatinine ratio (ACR) of 3 mg/mmol or more should be offered an angiotensin receptor blocker (ARB) or an angiotensin converting enzyme (ACE) inhibitor, titrated to the highest licensed & tolerated dose"

The NICE appraisal committee determined that people with a baseline ACR of 3 to 30 mg/mmol will experience fewer cardiovascular events and events relating to CKD progression than people with a higher ACR. Because of this, SGLT2 inhibitors would prevent fewer events for this group in absolute terms, even if the relative effect was the same. Economic modelling showed that SGLT2 inhibitors were still likely to be both more effective and cost saving in people with a baseline ACR of between 3 and 30 mg/mol compared with standard treatment.

The guideline calls for research on the effectiveness of SGLT2 inhibitors for people with a baseline ACR less than 3 mg/mmol as there is no evidence looking specifically at this group.

Draft recommendations have also been published on the *diagnosis and management of adults with type 1 diabetes.* The draft guidance advises that age or body mass index (BMI) alone should not be used to exclude type 1 diabetes. It must be kept in mind that other diabetes subtypes may be present and the diagnosis of type 1 diabetes should be reviewed at clinical reviews.

Diabetes-specific autoantibodies should be measured at the time of diagnosis, bearing in mind that these tests have the lowest rate of false negatives at that time. Serum C-peptide should not routinely be used to confirm a diagnosis of type 1 diabetes, however, in people with a negative diabetes-specific autoantibody result, and uncertain diabetes classification, non-fasting serum C-peptide can be used with a paired blood glucose. Serum C-peptide measurement can also be used to revisit the diabetes classification if there is doubt about the type 1 diagnosis, being mindful that the discriminative value of serum C-peptide to diagnose type 1 diabetes *increases* the longer the test is conducted after initial diagnosis.

The guidance now recommends that patients should be offered a choice of real-time continuous glucose monitoring (CGM) or intermittently scanned continuous glucose monitoring (isCGM) based on their needs and preferences. The cheapest device should be offered in the first instance. If a person is unable or does not wish to use any real-time CGM or isCGM device, capillary blood glucose monitoring should be used.

NICE has also published draft guidance on the *diagnosis of type 1 and 2 diabetes in children and young people.* The guidance includes updated recommendations on CGM for this age group. It is now recommended that all children and young people with type 1 diabetes be offered the choice of real-time CGM, accompanied by education. Paediatric patients (aged ≥4 years) who are unable or prefer not to use real-time CGM should be offered isCGM.

Factors to consider when choosing a device include whether the device provides predictive alerts or alarms and whether these need to be shared with anyone else, the ease of use (including for people with limited dexterity), and how often the device needs to be calibrated. It is also important to consider patient factors, including their insulin regimen and type of insulin pump, as not all devices integrate with pumps as part of a hybrid closed loop or insulin suspend function. Other factors to consider include sports participation, device sensitivity and cosmetic aspects. If a child or young person is unable or does not wish to use any real-time CGM or isCGM device, capillary blood glucose monitoring should be offered. The final recommendations are expected to be published at the end of March next year.

O'Shea D (2021) NICE Updates Recommendation on the Management of Diabetes. *Medscape*, 26 November, 2021.

100 Years of Insulin, but Millions Still Without Access

It's the 100th anniversary of the discovery of insulin. I'm going to talk about what I think is interesting in its history and then touch on the issues that we currently have with regard to people using insulin.

Insulin Discovered. The pancreatic islet cells (the islets of Langerhans) were discovered by a medical student named Langerhans in 1869. In 1889, a pancreatectomy in a dog produced diabetes. Subsequently, multiple investigators tried to produce extracts that lowered blood glucose and helped treat diabetes in pancreatectomised dogs. But the extracts that they created were too toxic to be administered to patients.

In 1921, the team of Frederick Banting, Charles Best, and James Collip were working in the department of physiology laboratory, headed by Dr John Macleod, at the University of Toronto. They were able to make pancreatic extracts, first from dogs and then from cattle, which they found could be used to safely treat humans with type 1 diabetes who had previously been dying of their disease. From the beginning, these investigators were really altruistic. In 1921, Frederick Banting said, "*Insulin does not belong to me. It belongs to the world*." The first human to get the insulin extract was Leonard Thompson in January 1922. He was 14 years old and dying of type 1 diabetes. He was incredibly skinny and very close to death. His first reaction to being given insulin was a bad one. He had a severe allergic reaction to the impurities in the insulin, so it was quickly modified and then given to him again, and he did well. Unfortunately, he lived only another 12 years, dying at the age of 26 of pneumonia. Ironically, his timing was impeccable with regard to the discovery of insulin. But his timing with regard to the discovery of antibiotics wasn't quite the same, because Fleming only discovered penicillin in 1928 and antibiotics weren't widely available until 1940.

The first US citizen to receive insulin was Elizabeth Hughes Gossett. She was the daughter of the governor of New York, Charles Hughes, and she went up to Toronto to get the insulin. She lived to the age of 73, had three children, and died in 1981 of cardiovascular disease. She was true proof of the concept that exogenously administered insulin can help treat type 1 diabetes.

Insulin Marketed. Banting, Best, and Collip were given a patent in the US for their insulin, and they sold the rights back to the University of Toronto for a dollar because they wanted the insulin to be available to pharmaceutical companies to manufacture and distribute widely so people could benefit. The first partner to manufacture insulin was Lilly. The first insulin was called isletin, and it was much like the regular insulin of today. You had to give it as much as four times daily if you really want to mimic physiology. Back then, it was administered with large, reusable glass syringes and needles.

In 1923, Banting and Macleod received a Nobel Prize in medicine. However, Best and Collip were not included in this award. Isletin was regular insulin, but it wasn't long-acting or short-acting insulin. It was sort of in the middle. So researchers went on to try to make this molecule better. The first thing they did was to add the protein named protamine, because this prolonged the activity of the insulin. The first protamine-based insulin was called PZI. Then we had NPH insulin, which we have to this day and it's widely available. Then we had the lente series of insulin, and in particular ultralente insulin, which was the first truly very long-acting insulin on the market. In the 1980s, recombinant human insulin was developed, and finally, we now have insulin analogues. The real benefit of the insulin analogues that we currently have on the market is the fact that the long-acting insulin analogues are more stable and seem to cause less hypoglycaemia than prior insulin analogues.

Insulin Is Out of Reach for Some. These have all been really great advances, but we have a long way to go. One of the biggest problems is access to insulin. I work in an underresourced part of Los Angeles. I see people who have only intermittent access to insulin or who have to ration their insulin, and they have A1c levels well above 10%. Yes, insulin keeps them alive, but they develop complications. I see all of the complications of diabetes in people in their 20s and 30s. We really aren't treating these people well.

And insulin alone is clearly not enough to make a big difference in the treatment of type 1 diabetes. To treat type 1 diabetes, we need the whole bundle. We need to be able to educate people. We need to give them tools. We need to give them support. We need to give them medical care. We need to give them psychological care. So the biggest barrier now is *access*, and inherent in that is the cost of insulin. Insulin production is in the hands of three large multinational pharmaceutical companies, and they account for 90% of the insulin market. A lot has been written about the high cost of insulin in the United States. There are many reasons for this, and I don't have time to go into detail about them. Suffice to say that many of us, and many different advocacy groups are working on this issue so patients can afford their insulin.

There are countries around the world, such as Canada, where you can get insulin at an affordable price. But there are many other countries, both middle and low-income countries, where insulin is unaffordable for the people who live there. It's very important to think globally. Worldwide, it is estimated that there are 30 million people who need insulin but can't afford it. Because of the cost and access issues, the World Health Organization just published its new edition of the list of essential medicines that should be available worldwide, and on that list are long-acting insulin analogues. It is hoped that this will result in more quality-assured biosimilar insulins entering the market, so there's more competition, which enables the price to be reduced, and insulin will be more widely available around the world. So even though I am incredibly happy that we have insulin - I don't know where we'd be without it - I also know that we still have many steps to take until insulin is readily accessible around the world and it is used in a way to provide optimal benefit to all people who need it. Thank you.

Any views expressed above are the author's own and do not necessarily reflect the views of WebMD or Medscape.

Anne L. Peters. 100 Years of Insulin, but Millions Still Without Access, *Medscape*. December 2021

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'Milestone' in Stem-Cell-Based Islet Replacement for Type 1 Diabetes

NEW YORK (Reuters Health) - Interim results from an ongoing multicentre clinical trial show that implanted pluripotent stem-cell-derived endocrine progenitor cells can secrete insulin in people with type 1 diabetes. This is "an important milestone for the field of human pluripotent stem cell (PSC)-derived cell replacement therapies as it is one of the first to report cell survival and functionality one year after transplantation," write Drs. Eelco de Koning and Francoise Carlotti of Leiden University Medical Center, the Netherlands, in an editorial in *Cell Stem Cell*.

"A landmark has been set. The possibility of an unlimited supply of insulin-producing cells gives hope to people living with type 1 diabetes," they write. The results were published this week in two companion papers in *Cell Stem Cell* and *Cell Reports Medicine*. In the *Cell Stem Cell* paper, Dr. Timothy Kieffer of the University of British Columbia and colleagues report an interim analysis of 15 people with type 1 diabetes who received subcutaneous implants of pancreatic endoderm cells (PEC) macroencapsulated in non-immunoprotective ("open") devices, which allowed for direct vascularisation of the cells. All patients underwent an immunosuppressive regimen used commonly in donor islet transplant procedures.

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The PEC implants, being developed by ViaCyte, were well tolerated with no teratoma formation or severe graft-related adverse events, and patients developed "meal-responsive insulin secretion post-implantation and retrieved grafts contained cells with a mature beta-cell phenotype," Kieffer and colleagues report. During one year of follow-up, recipients had 20% reduced insulin requirements and spent 13% more time in target blood-glucose range, the researchers say.

In the companion paper in *Cell Reports Medicine*, Dr. Howard Foyt of San Diego, California-based ViaCyte and colleagues report detectable engraftment and insulin expression in 63% of devices explanted from trial subjects at three to 12 months after implantation. "Initial data suggest that pluripotent stem cells, which can be propagated to the desired biomass and differentiated into pancreatic islet-like tissue, may offer a scalable, renewable alternative to pancreatic islet transplants," write Dr. Foyt and colleagues.

"The present study demonstrates definitively for the first time to our knowledge, in a small number of human subjects with type 1 diabetes, that PSC-derived pancreatic progenitor cells have the capacity to survive, engraft, differentiate, and mature into human islet-like cells when implanted subcutaneously," Dr. Foyt added in a news release.

"Regarding safety, most (severe) adverse events were associated with the use of immunosuppressive agents, which is not unexpected and similar to allogeneic solid organ transplantation. It further emphasizes the life-long use of immunosuppressive agents as a major hurdle for wider implementation of allogeneic cell replacement therapies," Dr. de Koning and Dr. Carlotti note in their editorial. They caution that many questions remain unanswered.

"The clinical road to wide implementation of stem cell-derived islet replacement therapy for type 1 diabetes is likely to be long and winding. Until that time, donor pancreas and islet transplantation will remain important therapeutic options for a small group of people. But an era of clinical application of innovative stem-cell based islet replacement therapy for the treatment of diabetes has finally begun,"

Ramzy A et al. (2021). Implanted pluripotent stem-cell-derived pancreatic endoderm cells secrete glucose-responsive C -peptide in patients with type 1 diabetes. *Cell Stem Cell,* 28 (12): 2047-2061 (https://bit.ly/3dfGM5q) and
Shapiro AMJ et al. (2021). Insulin expression and C-peptide in type 1 diabetes subjects implanted with stem cell-derived pancreatic endoderm cells in an encapsulation device. *Cell Reports Medicine*, 2 (12): 100466 (https://bit.ly/3DiJwd4).