

Antibiotic Use Linked to Increased Risk for Type 2 Diabetes

Miriam E Tucker | August 27, 2015

Antibiotic use was associated with an increased risk for type 2 diabetes in a new population-based, case-control study.

The findings were published online August 27, 2015 in the *Journal of Clinical Endocrinology and Metabolism* by Kristian Hallundback Mikkelsen, MD, a PhD student at the Center for Diabetes Research, Gentofte Hospital, University of Copenhagen (Hellerup, Denmark) and colleagues.

Data from three national Danish registries revealed that prior exposure to antibiotics was associated with a 53% increased risk of developing type 2 diabetes. The finding could mean that antibiotics play a direct causal role in type 2 diabetes or that people with as-yet-undiagnosed diabetes may have a greater risk for infection and therefore are more likely to use antibiotics.

"Both interpretations are supported by the literature and could contribute to the observed associations," Dr Mikkelsen told *Medscape Medical News*.

Clinically, the findings add a new argument to the current movement toward less frequent and more judicious use of antibiotics. "Microbiologists frequently remind clinicians not to overuse antibiotics because of the growing resistance problems and inadequate development of new antibiotics. If it appears that antibiotics also have long-term and potentially negative metabolic adverse effects, it of course puts additional weight behind a strict policy for antibiotics prescribing and selling," he noted.

Asked to comment, Martin J Blaser, MD, the Muriel and George Singer Professor of Medicine, professor of microbiology, and director of the Human Microbiome Program at New York University Langone Medical Center, New York, called this an "important paper" and a "very well-conducted large-scale study" that provides further evidence of the importance of gut microbiota in human health and disease.

"The results are consistent with a growing body of data that antibiotics affect metabolism through their 'collateral' effects on the microbiome," Dr Blaser said, noting that the findings are in line with those of a previous population-based study in the United Kingdom that also found an association between antibiotics and diabetes.

Greatest Effect Seen With Bactericidal, Narrow-Spectrum Antibiotics

The study used data from three national Danish databases — the Danish National Registry of Patients, the Danish National Prescription Registry, and the Danish Person Registry — which cover nearly all 5.6 million inhabitants of Denmark.

The investigators identified 170,504 individuals who received an incident prescription of a glucose-lowering agent during 2012 and matched them by age and gender to 8 (total 1,364,008) people without diabetes. The entire study population had a median age 62 years and 52% were male.

They analyzed data on antibiotic use going back to 1995. To minimize the bias that those who went on to develop diabetes might also have a higher likelihood of infection prior to diagnosis, the investigators excluded all antibiotic prescriptions filled less than 6 months before the date of the first diabetes medication prescription (or matched index date for the controls) and also analyzed the data going back 3 years prior.

The average number of antibiotic prescriptions redeemed per year was 0.8 for the type 2 diabetes group, compared with 0.5 for the controls. Just 9% of the cases and 13% of the controls did not fill any antibiotic prescriptions prior to their index date.

Overall, the odds ratio for developing type 2 diabetes for those who had filled any antibiotic prescription compared with none was 1.53. Compared with having filled two to four prescriptions with zero to one prescription, the odds ratio was 1.21. When the exclusion period for antibiotic prescriptions was extended to 3 years before the index date, the odds ratio dropped only slightly, to 1.43.

The odds ratios were slightly higher for narrow-spectrum and bactericidal antibiotics than for broad-spectrum and bacteriostatic antibiotics, but all the odds ratios for individual antibiotics were significantly increased, except for clindamycin.

There was a dose-response relationship between antibiotic exposure and type 2 diabetes for all antibiotics, and this was also slightly stronger for the narrow-spectrum/bactericidal agents. The relationship didn't change when the groups were stratified by age, gender, or observation period.

The increased exposure to antibiotics in those who went on to develop diabetes was seen up to 15 years prior to the index date, with a similar pattern seen for all classes of antibiotics, the authors report.

Which Explanation Is More Likely?

Dr Mikkelsen told *Medscape Medical News* that there is evidence for both hypotheses about the mechanism behind the association. Compared with controls, people with diabetes may have more skin infections or common airway infections, and these are normally treated with narrow-spectrum antibiotics in Denmark. However, "whether the same accounts for patients with type 2 diabetes 15 years before they become [diagnosed] is unknown," he said.

Evidence for a direct effect of antibiotics is seen in animal models, where all kinds and types of antibiotic produce a growth-promoting effect, he noted.

Dr Mikkelsen's institution has recently conducted a small interventional study on the effect of broad-spectrum antibiotics on gut hormone secretion and glucose homeostasis in healthy, glucose-tolerant adults, while other groups are conducting randomized clinical trials on the metabolic effects of antibiotics.

"I think more randomized clinical trials with long-term follow-up are needed before we can [come a conclusion] on the possibility for antibiotics-induced metabolic adverse effects," he said.

Dr Blaser told *Medscape Medical News*, "Both explanations are possible.... That is why we do studies in mice, so we can test hypotheses directly. But mice aren't people, and so it is important to conduct epidemiologic studies like this. ... My opinion is that the evidence is mounting that antibiotics have long-term effects on disease risk."

Dr Mikkelsen holds stocks in Chr Hansen and Probi; disclosures for the coauthors are listed in the article. Dr Blaser has no relevant financial relationships.

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