Circumcision alters penis microbiome, could explain HIV protection

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Circumcision drastically alters the microbiome of the penis, changes that could explain why circumcision offers protection against HIV and other viral infections. In a study to be published on April 16 in *mBio*, the online open-access journal of the American Society for Microbiology, researchers studied the effects of adult male circumcision on the types of bacteria that live under the foreskin before and after circumcision. By one year post-procedure, the total bacterial load in that area had dropped significantly and the prevalence of anaerobic bacteria, which thrive in locations with limited oxygen, declined while the numbers of some aerobic bacteria increased slightly.

"The change in the communities is really characterized by the loss of anaerobes. It's dramatic," says the corresponding author, Lance Price of the Translational Genomics Research Institute (TGen) in Flagstaff, Arizona and George Washington University in Washington, DC. "From an ecological perspective, it's like rolling back a rock and seeing the ecosystem change. You remove the foreskin and you're increasing the amount of oxygen, decreasing the moisture - we're changing the ecosystem," he continues.

Randomized controlled trials show that circumcision reduces the risk of HIV infection in men by 50-60% and reduces the risk of infection with human papillomavirus and herpes simplex virus type 2, but the biology behind these benefits is not well understood. It could be that the anatomy of the circumcised penis helps prevent infection, or it could be that changes in the microbiome confer protection, or some combination of

the two.

Using swab samples from a large circumcision trial in Uganda, Price and his colleagues at Johns Hopkins and TGen set out to determine whether circumcision significantly alters the penis microbial community. Using a quantitative technique called qPCR along with pyrosequencing to identify individual community members, the researchers compared samples from uncircumcised men with samples from circumcised men that were taken both before the procedure and one year later.

"There was a dramatic and significant change in the penis microbiome as a result of male circumcision," says Price. At the beginning, the microbiota of both groups of men were comparable. One year after their operation the bacterial load in all men had declined somewhat, but in circumcised men the decline was significantly greater than in the uncircumcised controls. And nearly all the bacterial groups that declined were strict anaerobes or facultative anaerobes. Overall, these changes amount to a reduced biodiversity in the microbiota.

"From a public health perspective the findings are really interesting because some of these organisms that are decreasing could cause inflammation," says Price. "We're used to thinking about how disrupting the gut microbiome can make someone more susceptible to an infection. Now we think maybe this disturbance [in the penile microbiome] could be a good thing - could have a positive effect," says Price.

Just what role the penile microbiome might play in HIV acquisition is not yet known, but studies suggest that genital bacteria may affect how susceptible the penis is to sexually transmitted viral infections. In uncircumcised men, high bacterial loads may activate cells in the foreskin called Langerhans cells, preventing them from carrying out their normal role in fending off viruses. Instead, these activated Langerhans cells betray the body, binding and delivering HIV particles

right to T-cells, where they can initiate an infection. Cutting back on the numbers of bacteria on the penis could, conceivable, prevent these Langerhans cells from becoming turncoats.

To follow up on this work, Price says he and his colleagues plan to address the question of whether the penile microbiome affects HIV transmission by studying possible links between changes in the microbiome and cytokine responses, signaling mechanisms that can activate the immune system.

To Price, this study has implications beyond circumcision. Understanding the changes in the microbiome following surgery could eventually lead to interventions that don't require a surgical procedure. "The work that we're doing, by potentially revealing the underlying biological mechanisms, could reveal alternatives to circumcision that would have the same biological impact. In other words, if we find that it's a group of anaerobes that are increasing the risk for HIV, we can find alternative ways to bring down those anaerobes," and prevent HIV infection in all sexually active men, says Price.

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