Male Circumcision and HIV: Do All Roads Lead to Rome?

The evidence that male circumcision (MC) reduces the risk of human immunodeficiency virus (HIV) in men is substantial,[1-3] but a biologically plausible explanation for this effect remains elusive. The pathogenesis is more complex than previously thought, and may involve several different mechanisms acting in concert to activate mucosal immunity and disrupt the barrier function of the epithelium. Earlier studies focused on the differential thickness between the inner and outer keratin layers. Tissue studies have shown that the inner foreskin, frenulum, and urethra are less keratinized than the outer foreskin and glans.[4] There is also evidence of an increased density of HIV target cells (Langerhans cells, macrophages, and CD4 cells) in the foreskin.[5] It has been postulated that the thinner anatomical barrier between the dendritic projections of the Langerhans cells and the vaginal secretions at the inner foreskin allow a more effective uptake of the virus. Other studies, however, challenge this theory. Analyses of the foreskins of Chinese men and boys following elective circumcision have found a thicker inner foreskin compared to the outer surface in adults and children with a history of penile infections.[6] Another recent study has reported no significant difference in the thickness between the inner and outer keratin layers, using a novel staining technique of the tissues.[7] All these investigations are limited by small sample sizes, lack of standardized technique to measure keratin, and a possible confounding effect of recurrent infection. Thus, the barrier theory needs further study.

The size of the foreskin and the moist environment of the uncircumcised penis may also contribute to an increased risk of HIV acquisition. A retrospective cohort study conducted in Uganda, has reported that men with a larger foreskin surface area are more likely to become infected than men with smaller foreskins.[8] A wet subpreputial space, linked to a higher HIV prevalence,[9] provides an optimal milieu for the growth of commensal microbial flora, which may contribute to local inflammation and activation of immune cells. Price *et al.*,[10] examined and characterized the penile microbiota of HIV-negative men by gene pyrosequencing, before and after MC. They reported a significant reduction in the number of anaerobic bacteria in the penile mucosa following MC, and postulated that the anoxic environment of the subpreputial space in uncircumcised men may support the growth of anaerobes, capable of inducing mucosal inflammation and activation of the Langerhans cells.

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The study by Schneider *et al.*, published in this issue of the journal, expands our knowledge of the penile microbiota. In this study, swab cultures were obtained from the coronal sulcus and the proximal urethra of 315 Indian men. These men belonged to one of the following three groups: Hospitalized HIV-infected patients (n=150); hospitalized patients with tuberculosis (n=115); and ambulatory patients presenting to a fertility clinic (n=50, controls). The authors found that 60% of the participants were colonized with a bacterial pathogen. *Staphylococcus aureus* (SA) (41.6%) and *Enterococci* (3.5%) were the most commonly cultured gram positives, while the gram negatives accounted for 22.9% of the isolates. Anaerobes were only 1.6% of the total. In the multivariable analyses, uncircumcised men were almost twice as likely to be colonized with a gram-positive organism and almost three times more likely to be colonized with a gram-negative pathogen than circumcised men. Interestingly, when analyzed by individual groups (HIV, TB, and controls), the HIV- and TB-infected individuals were more likely to be colonized with gram-negative bacteria, but there was minimal difference in the rates of gram positives between the different groups.

The finding of a larger number of bacteria in uncircumcised men in this study is not surprising. However, the high proportion of SA is intriguing and has been reported elsewhere.[11] This pathogen, a frequent skin colonizer and producer of cytotoxins and exoenzymes, could elicit a local inflammatory response capable of activating mucosal immune cells and potentially contribute to HIV acquisition. Some issues, to determine the role of this bacterium in the pathogenesis of HIV acquisition, should be considered in future studies; for instance, how does hospitalization change someone's indigenous microbiota? The majority of subjects in the current study were chronically ill, hospitalized patients, who were expected to be more frequently colonized with SA. Also, how does ongoing antibiotic administration modify the indigenous microbiota? A non-trivial number of subjects, that is, those infected with TB and HIV, with lower CD4 counts, were

receiving rifampicin or trimethoprim-sulfamethoxazole, both drugs active against SA. A reader could argue that the true prevalence of gram positives could be even higher than reported in the present study if antimicrobial administration was controlled in future study designs.

The contribution of the penile microbiota to the pathogenesis of HIV acquisition is an interesting pathway to explore, as we seek to explain the protective effect of MC. This study adds a provocative piece to this very complicated puzzle.

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