Metformin May Help Shrink HIV Viral Reservoir

The diabetes drug could potentially be used as part of a “shock and kill” strategy to achieve a functional cure.

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Metformin, a medication used to treat type 2 diabetes, may help the immune system recognize HIV and reduce the viral reservoir, according to study results published in Cell iScience. Other research suggests that metformin may also improve immune recovery when added to antiretroviral treatment.

Antiretroviral therapy (ART) can keep HIV replication suppressed indefinitely, but the virus inserts its genetic blueprints into the DNA of human cells and establishes a long-lasting reservoir that the drugs can’t reach. This integrated HIV DNA lies dormant in resting T cells during treatment, but it can start churning out new virus when antiretrovirals are stopped, making a cure nearly impossible.

Metformin (Glucophage and generic equivalents), an mTOR inhibitor, is a widely used medication that promotes insulin activity, decreases glucose production in the liver and helps control blood sugar levels. The mTOR (mechanistic target of rapamycin) pathway plays a role in both glucose metabolism and T-cell growth and differentiation. Metformin promotes weight loss, may improve fatty liver disease and other metabolic problems, has anti-inflammatory effects and has shown activity against some viruses, including SARS-CoV-2 (the coronavirus that causes COVID-19). The oral drug is generally well tolerated, but it can cause side effects including gastrointestinal symptoms.

Augustine Fert, PhD, of the University of Montreal Hospital Research Center, and colleagues previously showed that metformin reduced mTOR activation and HIV transcription in CD4 T-cells and decreased systemic inflammation in nondiabetic people living with HIV. Chronic inflammation contributes to numerous comorbidities, including cardiovascular disease, cancer and dementia.

In the new study, the researchers explored how metformin affects the HIV replication cycle and viral reservoir. They used a viral outgrowth assay to analyze CD4 T cells collected from 13 HIV-positive people on antiretroviral therapy. All but one were men, most were white and all had clade B HIV, the type most common in North America and Europe.

When cells were exposed to HIV in the laboratory, metformin led to an increase in the number of productively infected CD4 cells, meaning they contain intact virus capable of replicating. But it also reduced the release of new viral particles from these cells. This coincided with higher expression of an HIV release factor dubbed BST2 (tetherin), which binds newly produced virus to the cell surface and prevents it from exiting, as well as a survival factor known as Bcl-2, which inhibits cell suicide.

Together, this led to improved recognition of productively infected CD4 helper T cells by broadly neutralizing HIV envelope antibodies. Although this study did not look specifically at CD8 killer T cell responses, prior research has shown that metformin appears to increase their activity against cancer cells, so it might also enhance the activity of CD8 cells that target HIV.

“Metformin exerts pleiotropic effects on post-integration steps of the HIV-1 replication cycle and may be used to accelerate viral reservoir decay in ART-treated people with HIV,” the study authors concluded. (Pleiotropic means that a drug works by multiple mechanisms.)

These findings suggest that by reactivating infected CD4 cells in the viral reservoir, metformin might be used as part of a “shock and kill” functional cure strategy to flush out the virus and make it recognizable to the immune system and susceptible to antiretrovirals.

The researchers now plan to launch a clinical trial to test metformin in people living with HIV. As a limitation, they noted that oral metformin mostly acts in tissues such as the intestines and liver, so it may not reach peripheral blood CD4 cells throughout the body.

In another report, Silvere Zaongo, PhD, and Yaokai Chen, MD, of the Chongqing Public Health Medical Center in China, reviewed evidence about immunological nonresponders—people who do not experience adequate immune recovery and maintain a low CD4 count despite viral suppression on antiretroviral therapy.

As described in the Chinese Medical Journal, they found that immune cell exhaustion, combined with chronic inflammation and a disturbed gut microbiome, may contribute to incomplete immune recovery. Prior studies in the literature suggest that metformin has properties that may help ameliorate all three factors.

“In light of evidence discussed in this review, it can be seen that metformin may be of particularly favorable use if utilized as adjunctive treatment in immunological nonresponders to potentially enhance immune reconstitution,” the authors wrote. “The approach described herein may represent a promising area of therapeutic intervention, aiding in significantly reducing the risk of HIV disease progression and mortality in a particularly vulnerable subgroup of HIV-positive individuals.”

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