

Cystic Fibrosis Research News

Title:

Sweat chloride reflects CFTR function and correlates with clinical outcomes following CFTR modulator treatment

Lay Title:

How sweat chloride levels relate to health improvements with CFTR modulators

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What was your research question?

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People with cystic fibrosis (CF) have salty sweat because the CF transmembrane conductance regulator (CFTR) protein does not work properly. Medicines called CFTR modulators help the protein work better, lowering sweat salt levels. We asked if people taking modulators who had lower sweat salt levels had more improvement in symptoms of CF.

Why is this important?

People with CF with higher sweat chloride levels (saltier sweat) experience severe symptoms of the disease and have shorter lifespans compared to those with lower sweat chloride levels (less salty sweat). After starting treatment with a CFTR modulator, sweat chloride levels go down. Sweat salt levels may show how much better the CFTR protein works. Some people's sweat chloride levels are lower but still over the diagnostic cut-off for CF (≥ 60 mmol/L), while others reach normal levels (< 30 mmol/L). Understanding how these levels relate to symptoms of CF helps determine the necessary reduction to prevent CF-related problems.

What did you do?

We took lung cells from people with different CF variants. In the laboratory, we measured how much salt moved across these cells with and without CFTR modulators. We also measured sweat chloride levels in people with CF and compared them to the salt movement in the laboratory samples with the same CF variants. Next, we reviewed clinical studies of three CFTR modulators: tezacaftor-ivacaftor, elxacaftor-tezacaftor-ivacaftor, and an experimental drug VX-659-tezacaftor-ivacaftor. We compared sweat chloride levels in people with CF taking these CFTR modulators to improvements in lung function, nutrition (body mass index), frequency of respiratory illness (pulmonary exacerbations), and respiratory symptoms.

What did you find?

In the laboratory, we found that the amount of salt that moved across the lung cells corresponded to the sweat chloride levels in people with CF who had the same CF variant and were treated with the same CFTR modulator. In clinical studies, people with CF with lower sweat chloride levels (< 60 mmol/L) after CFTR modulator treatment experienced better and more stable lung function over time, improved nutrition (body mass index), and a lower frequency of respiratory illness (pulmonary exacerbations) and respiratory symptoms than those with higher sweat chloride levels.

What does this mean and reasons for caution?

Sweat chloride levels in people with CF relate to how well the CFTR protein moves salt (chloride) across lung cells in the laboratory. Scientists can use this to predict how well a CFTR modulator might work in people. People on modulators who have lower sweat chloride levels



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may do better than people whose sweat chloride levels are still in the CF range. Even though modulators work very well, sweat chloride levels stay in the CF range for some people, suggesting that new modulators may be needed to better prevent complications from CF.

What's next?

As new CFTR modulators are developed, more people with CF may reach lower sweat chloride levels, leading to improvements in health outcomes. Longer studies may help us understand the benefits of normal sweat chloride levels in people with CF and identify the best goals for CFTR modulator treatment.

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