

# Cystic Fibrosis Research News

**Title:** CFTR modulator therapy alters plasma sphingolipid profiles in people with cystic fibrosis

**Lay Title:**

CFTR modulator therapy alters sphingolipid profiles in blood from people with cystic fibrosis

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**What was your research question?**

Sphingolipids, in particular ceramides, play an important role in the regulation of inflammation and infection in cystic fibrosis (CF). CFTR modulator therapy might influence the sphingolipid composition in people with CF (PWCF).

**Why is this important?**

Sphingolipids such as ceramides and sphingosine are important for the structure of cell membranes in the human body, and are also involved in the transfer of information in a cell (cell signaling processes). Changes in the composition of ceramides, indicated by an elevated ratio of ceramide subtypes called C16Cer/ C24:0Cer, have been linked to inflammation, disease severity and susceptibility to infection in PWCF. Furthermore, a lack of sphingosine has been found in airway epithelial cells from PWCF. Targeting the sphingolipid metabolism represents a potential therapeutic approach in CF.

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## What did you do?

Sphingolipid profiles were retrospectively analyzed in blood from 112 PWCF who were not receiving CFTR modulator therapy, 96 healthy controls as well as from 25 PWCF before and after treatment with the CFTR modulator elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) using an analytical technique called liquid chromatography-tandem mass spectrometry (LC-MS/MS). The resulting blood profiles were compared with clinical information that was collected about the study participants.

## What did you find?

Sphingosine levels were reduced in PWCF and accurately distinguished PWCF from healthy controls. Treatment with ELX/TEZ/IVA was associated with a decrease in levels of various ceramide subtypes, C16Cer, C18Cer and C20Cer as well as C24:1Cer. In parallel, blood levels of the most abundant ceramide subtype, C24:0Cer, and sphingosine-1-phosphate increased with treatment. Consequently, the ratio of ceramide subtypes C16Cer/ C24:0Cer decreased. Sphingolipid levels showed limited correlations with clinical information.

## What does this mean and reasons for caution?

Blood sphingolipid levels appear to be altered by ELX/TEZ/IVA therapy. The ratio of ceramide subtypes C16Cer/ C24:0Cer has been linked to inflammation in CF. Therefore, the decreased ratio detected with CFTR modulator treatment is a favourable outcome. Sphingosine levels accurately distinguish people with CF from healthy controls and might serve as a diagnostic test.

## What's next?

Our results need to be confirmed in samples from other body compartments, such as lung tissue or bronchoalveolar lavage fluid. It remains unclear to what extent the sphingolipid composition is rebalanced by highly effective CFTR modulator therapy. Thus, further data from experimental and clinical studies are needed that examine the additive effects of sphingolipid therapies in the era of ELX/TEZ/IVA therapy. Our results do not exclude that potential therapies which specially target sphingolipid metabolism might have a beneficial effect in addition to CFTR modulator therapies.

## Original manuscript citation in PubMed

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