Common genetic variation could make home dialysis less effective for some patients

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RESEARCH SUMMARY

AQP1 Promoter Variant, Water Transport, and Outcomes in Peritoneal Dialysis

Morelle J et al. DOI: 10.1056/NEJMoa2034279

CLINICAL PROBLEM

The efficiency of peritoneal dialysis depends on ultrafiltration — the ability to remove excess water from the body. Among patients starting treatment with peritoneal dialysis, there is broad variability in ultrafiltration. Such variability influences dialysis prescriptions and outcomes, but its causes are poorly understood. Variation in *AQP1*, the gene encoding aquaporin-1, has been proposed as one contributing factor.

STUDY DESIGN

Researchers examined data from 1851 adults in seven cohorts receiving peritoneal dialysis for kidney failure. Blood samples were analyzed for *AQP1* variants, and results of peritoneal transport testing were used to examine whether the identified *AQP1* variants were associated with ultrafiltration; peritoneal solute transfer rate was also assessed. Clinical outcomes, including a composite of death or technique failure (i.e., transfer to hemodialysis), were assessed.

RESULTS

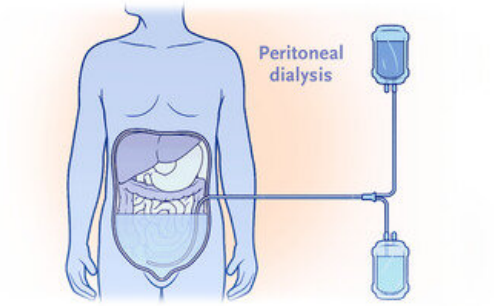
Ultrafiltration: Among the *AQP1* variants identified, the common promoter variant rs2075574 was significantly associated with peritoneal water transport. In particular, patients with the TT genotype at rs2075574 (14% of the cohort) had lower net ultrafiltration and sodium sieving levels than patients with the CC genotype, despite having a similar peritoneal solute transfer rate.

Clinical Outcomes: During a mean follow-up of 944 days among 898 patients, those with the TT genotype had a higher incidence of the composite of death or technique failure than those with the CC genotype. This difference was largely attributable to a higher incidence of death from any cause with the TT genotype.

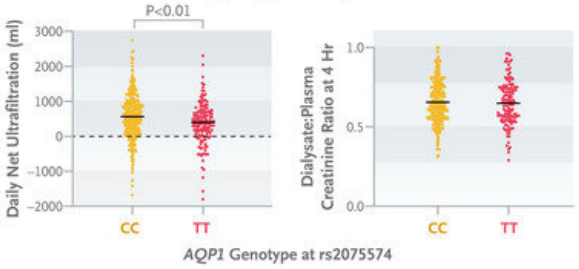
LIMITATIONS AND REMAINING QUESTIONS

- The study was retrospective, and patients' fluid volume status was not assessed. The relationship of the rs2075574-associated decrease in ultrafiltration with fluid overload and mortality requires further study.
- Whether adjustment of the patient's peritoneal dialysis prescription may attenuate the risk posed by the rs2075574 variant remains unknown.

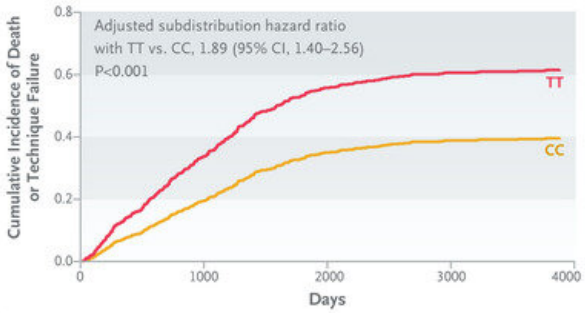
Links: Full Article | NEJM Quick Take | Editorial



Daily Net Ultrafiltration and Peritoneal Solute Transfer Rate According to *AQP1* Genotype at rs2075574



Risk of Composite Outcome According to *AQP1* Genotype at rs2075574



CONCLUSIONS

In patients undergoing peritoneal dialysis, a common *AQP1* variant was associated with decreased ultrafiltration and an increased risk of the composite of death or transfer to hemodialysis.

Research Summary. Credit: DOI: 10.1056/NEJMoa2034279

A common variation in a specific gene could make home kidney dialysis treatments less effective for some patients, leading to worse outcomes and even death in some cases.

Home dialysis therapies such as peritoneal dialysis have increased in popularity in recent years, in both developed countries like the United States and developing countries.

Home therapies like this are advantageous as they can reduce the cost to countries' health services, as well as making these treatments more accessible for patients living in remote or rural areas. They also require less support from trained medical or technical staff.

But new research co-led by Keele's Professor Simon Davies has found that such treatments may be less effective if patients have a common variation in a gene known as AQP1 (Aquaporin-1).

Peritoneal dialysis is dependent on a process called ultrafiltration—the ability to remove excess water to restore normal body-fluid status, as well as to clear waste substances from the body, a process which is governed by genes including AQP1.

Publishing their findings in the *New England Journal of Medicine*, the international research team found that variations in the AQP1 gene affected how successfully patients' bodies performed ultrafiltration, which subsequently affected the outcome of their treatment.

They used data from over 1800 peritoneal dialysis patients, first assessing the impact that different variations in AQP1 may have on the patients' treatment, confirming observations made in the laboratory. Having discovered the important variant, they then validated their

findings in 898 patients to assess its impact on survival. The 15% of patients with the variant experienced significantly worse outcomes.

Simon Davies, Professor of Nephrology and Dialysis Medicine at Keele University said: "This is the first time that a single gene has been shown to determine clinical outcomes in people on dialysis. We have suspected for some time that there are important differences between people in how well they can remove fluid using peritoneal dialysis.

"Now that this is more clearly understood, clinicians will be able to recognize this problem earlier and make quite simple prescription changes to prevent the increased mortality risk. I am especially proud of this work and the part played by Keele, including my colleague Mark Lambie and previous Ph.D. student, Zanzhe Yu, who contributed the data from China."

More information: Johann Morelle et al, AQP1 Promoter Variant, Water Transport, and Outcomes in Peritoneal Dialysis, *New England Journal of Medicine* (2021). DOI: 10.1056/NEJMoa2034279

Provided by Keele University