Alpha1 MZ Foundation - Information & Research

News and Research Update

In our recent webinar, professor Gerry McElvany talked about "Z" polymers in serum, and explained that the amount of "Z" polymers is more related to the disease outcome compared to your AAT level. This newsletter offers additional information on this subject, based on research studies.

And as always, enjoy the ride!!

Circulating alpha-1 antitrypsin polymers as a determinant of liver and lung disease severity

1. Introduction

Alpha-1-antitrypsin (AAT) deficiency has long been clinically defined by serum AAT concentration, with disease risk stratified according to protective threshold levels. However, accumulating evidence from polymer-focused studies challenges this concentration-based paradigm. Instead, the polymerogenic behaviour of the SERPINA1 variants, particularly the Z allele, appears to determine clinical outcomes.

This shift in understanding is highly relevant for the MZ population, in which serum AAT levels often fall near or above the "outdated" previously established "protective" thresholds. Yet, substantial liver morbidity, bile acid dysfunction, gallstones, pregnancy cholestasis, and accelerated hepatic decompensation are increasingly recognized in this population.

2. Evidence that circulating AAT polymers reflects hepatic polymer burden

Early work by Tan et al. demonstrated that circulating AAT polymers are measurable in serum using polymer-specific monoclonal antibody ELISA assays and that levels decline following liver transplantation, strongly implying a hepatic origin.
Núñez et al. expanded this by quantifying circulating polymer levels across genotypes and correlating them with both liver stiffness and lung impairment.
More recently, Teckman et al. showed that polymer burden, not total AAT, predicts the development of portal hypertension in pediatric AATD.

3. The SS–MZ Comparison

Serum AAT levels between Pi*SS and Pi*MZ are similar; however, clinical outcomes differ as seen in the research studies of De Serres.
De Serres, 2002–2007, reviewed >70,000 genotyped individuals worldwide and found that:
Pi*SS individuals have no excess risk of COPD or airflow obstruction unless they smoke.

- Among *never-smokers*, SS had a COPD prevalence identical to MM controls.
- Among *ever-smokers*, SS risk increased slightly, but ***far less*** than the risk seen in MZ or the SZ populations.

We know that Pi*SS displays minimal polymer formation, while Pi*MZ demonstrates substantial Z-driven polymerization in the liver, including M-Z heteropolymers.
So the main difference between SS and MZ patients is the liver damage caused by the polymers. This means that the difference between the morbidities of the SS and MZ population must be explained by the polymer burden alone as the pathogenic determinant.

4. Interpretation and discussion

More recent, and still ongoing research shows that the severity of the polymer burden correlates with the severity of the morbidity burden.

This implies that the amount of polymers measured in serum would be an excellent biomarker, as it is a direct reflection of disease burden, and **not** the AAT serum level.

This seems to be a perfect fit with other research within the MZ population, which shows a list of morbidities that all points to liver malfunction. (the amount of polymer burden in the liver)

Some simple examples of morbidities in the MZ population:

- Intrahepatic cholestasis during pregnancy (20% of all ICP are MZs) clearly points to pericentral impairment in the liver.
- Gallstones and biliary tract morbidities (pointing to pericentral damage in the liver).
- Liver transplants: 10% of all liver transplants are MZs.
- The MZ liver decompensates 2 times faster.
- Endocrine disruptions and hormone imbalance again point to pericentral impairment.

This finally leads to the conclusion that the amount of polymerization stress over the whole liver lobule from periportal to pericentral (caused by the Recruitment Secretory Block in the MZ population) is the primary cause of the MZ morbidities, which can be measured by the level of polymers in serum. Determining the polymer level in serum would be a good measure to determine the MZ disease burden.

Click here to watch the video with professor McElvaney.

5. References

Tan L et al. Circulating polymers in α1-antitrypsin deficiency. Eur Respir J. 2014.

Núñez A et al. Association between circulating alpha-1 antitrypsin polymers and lung and liver disease. Respir Res. 2021.

Sark R et al. Plasma Alpha-1-Antitrypsin Polymers and Lung and Liver Disease. Biomolecules. 2022.

Balderacchi M et al. Quantification of circulating alpha-1-antitrypsin polymers associated with different SERPINA1 genotypes. Clin Chem Lab Med. 2024.

Teckman J et al. Biomarkers Associated with Future Severe Liver Disease in Children with Alpha-1-Antitrypsin Deficiency. 2024.

Support the Alpha1 MZ Foundation

If you value our newsletters and the work we do, please consider supporting the Alpha1 MZ Foundation. Every contribution, no matter the size, helps advance patient education, drive vital research, and strengthen our global movement toward a cure that will benefit you, your children, your family, and the 35 million Alpha1 MZ patients worldwide.

We're building something together — knowledge, hope, and a future for Alpha-1 MZ families. If our work matters to you, please help us keep going.

👉 Donate today on our website and help move us one step closer to a cure.

Your support truly makes a difference!