Identifying and preventing cardiovascular disease in patients with cystic fibrosis

Improving standards of care and new therapeutics means individuals with cystic fibrosis are living longer, but this brings an increased risk of non-communicable diseases, especially cardiovascular disease (CVD). To improve both longevity and quality of life, it is important to consider CVD risk and prevention in those living with cystic fibrosis.

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Cystic fibrosis is a multi-system disease, with manifestations including widespread inflammation, recurrent respiratory infections and gastrointestinal disease. Progressive respiratory failure is the primary cause of death. Life with cystic fibrosis has undergone dramatic changes over recent decades, with targeted interventions throughout childhood improving quality and length of life. However, the introduction of disease-modifying therapeutics in the past decade has been a game-changer: for the first time, children with cystic fibrosis are expected to live well into their fifth or sixth decade. The health challenges they will face are unknown, but with increased longevity come associated risks, including CVD. This represents a previously overlooked burden of illness for these individuals, as little consideration is given to the detection and prevention of CVD in current cystic fibrosis care.

Chronic disease and the cardiovascular system

The American Heart Association states that with optimal primordial and primary prevention, CVD is "largely preventable," and that earlier interventions are likely to be more effective. This paradigm is particularly relevant to those with cystic fibrosis, but it has yet to be incorporated into clinical care for this condition as it has in other chronic inflammatory conditions.

Cystic fibrosis shares similarities with many other chronic diseases linked with adverse cardiovascular health. Chronic obstructive pulmonary disease, suppurative lung disease and isolated respiratory infections in adults are associated with increased acute cardiovascular events. Rapidly declining lung function in general populations is linked to incidental heart failure and stroke[1]. Chronic inflammatory conditions including HIV, rheumatoid arthritis and systemic lupus erythematosus are also associated with increased risk of CVD[2]. It is unclear whether similar risks pertain to cystic fibrosis, but unique aspects of the disease might compound these risks, and the scant evidence to date is potentially concerning.

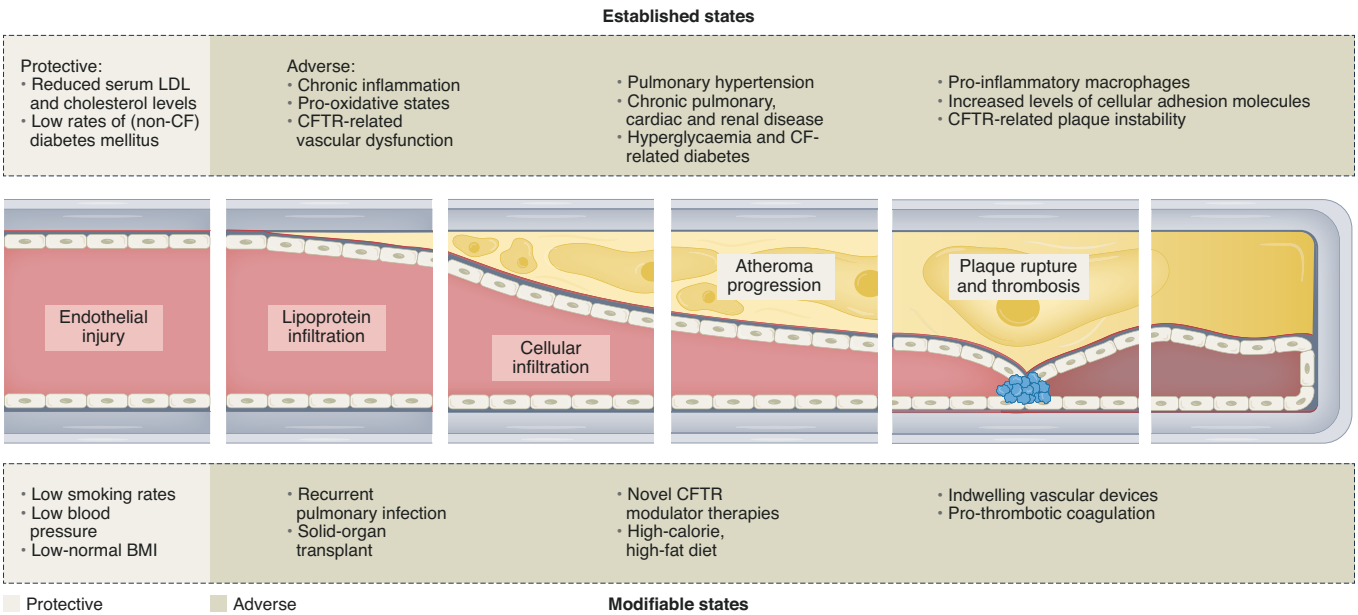

Fig. 1 | Sources of potential cardiovascular risk in people with cystic fibrosis. Atherosclerosis is a chronic inflammatory process; the rate and extent of development are determined by both traditional and novel cardiovascular risk factors. In people with cystic fibrosis, these risk factors might be affected by CFTR-protein deficit, chronic inflammation and systemic disease manifestations, or might result from therapeutic interventions. There are several possible modifiable risk factors in cystic fibrosis, but which are key and what the critical age is for maximal impact are still unknown. The introduction of novel CFTR modulator drugs might allow more established cardiovascular risk factors to be targetable and preventable. BMI, body mass index; CF, cystic fibrosis; LDL, low-density lipoprotein.

The changing landscape in cystic fibrosis

Autopsy studies in children with cystic fibrosis from the 1950s showed minimal early atherosclerosis, but these data are from children who usually died within their first decade of life and did not receive current treatments[3]. Neonatal screening is now widely implemented to diagnose cystic fibrosis, allowing treatment to be introduced even earlier in life. Malnutrition from pancreatic insufficiency has been managed with high-fat, high-calorie diets and pancreatic enzyme replacement, aiming for body mass indices at or above the 50th percentile. Precipitous declines in lung function and life-limiting pulmonary infections have been slowed or controlled with antibiotics and airway clearance physiotherapy. Finally, novel therapeutics targeting the cystic fibrosis transmembrane regulator protein (CFTR) defect are changing the natural history of the disease, with reports of improvement in lung function rather than just attenuation of further decline.

There is an increasing prevalence of phenotypes of cystic fibrosis that may increase the risk of CVD. Aging adult cohorts have more obesity, hypertension, cystic-fibrosis-related diabetes, and chronic kidney disease than do younger cohorts with cystic fibrosis, possibly related to specific diet and drug therapies[4,5]. Real-world studies of the cystic fibrosis diet show a predisposition to nutrition-poor foods, saturated fats and excessive sugar[6]. Early life mixed feeding, early weaning to solids and lifelong systemic and enteric antibiotics are likely to affect the gut microbiome and related metabolic functions[7]. Whether cystic-fibrosis-related dysbiosis leads to specific cardiovascular consequences is unknown, but the issue warrants investigation and might offer the potential for future therapeutic interventions. Finally, those treated with novel CFTR therapeutics show evidence of increasing body mass index, blood pressure and serum lipids, particularly low-density lipoprotein in those with cystic-fibrosis-related diabetes[8].

Cardiovascular risk in cystic fibrosis

Cystic fibrosis is well recognized to have cardiac sequelae, including pulmonary hypertension, right heart dysfunction and cardiomyopathies throughout the life course. Less is known about its impact on the systemic vasculature, with cardiovascular outcomes rarely reported in national cystic fibrosis registry data sets. A multi-centre cohort of adults with cystic fibrosis and SARS-CoV-19 infection ($n = 422$) reported that 22.5% had a history of ischaemic heart disease, suggesting that CVD might be under-reported in this population[9].

Childhood and adolescence represent critical periods in which atherosclerosis is potentially amenable to primordial and primary prevention. In people with cystic fibrosis, the development of atherosclerosis might be accelerated by increased chronic inflammation and disease-specific risk factors (Fig. 1).

Cystic fibrosis is characterized by chronic systemic and organ-specific inflammation. Pro-inflammatory states and exaggerated responses to infections might have cumulative adverse effects on the vasculature. These vascular changes include endothelial damage, deposition of low-density lipoprotein, smooth muscle cell proliferation and the development of atherosclerotic plaques. In mouse models, restoration of impaired CFTR function reduces total atherosclerosis, improves ischaemia–reperfusion injury after cardiac ischaemia and can transition existing vulnerable plaque to more stable phenotypes[10,11].

Several adverse preclinical cardiovascular risk phenotypes have been reported in people with cystic fibrosis. Parameters of endothelial function, including levels of cellular adhesion molecules, flow-mediated dilation and post-occlusive reactive hyperaemia, are abnormal in people with cystic fibrosis. Abnormal large arterial structure and function have been reported, with increased aortic root stiffness and carotid intima–medial thickness, the latter most evident in pancreatic-sufficient individuals[12]. There are increased prevalences of elevated pulse wave velocity and increased values of augmentation index (relative to those of the general public) in people with cystic fibrosis, particularly in those with pancreatic insufficiency and acute respiratory infection[13]. Microvascular changes, including cystic fibrosis diabetes-related retinopathy and chronic kidney disease, are also increasingly being recognized[13]. These phenotypes often present in childhood and together represent a burden of cardiovascular risk potentially predictive of later-life disease, somewhat analogous to those accompanying bronchiectasis or HIV infection. Interventions including antibiotics, CFTR modulators and novel anti-inflammatory therapies might mitigate these changes, but their effects on CVD risk are largely unknown. Solid-organ transplants, not infrequent in people with cystic fibrosis, carry additional risks for CVD, which might affect transplantation eligibility and outcomes[14].

Conclusions and future directions

If we are to further improve on the hard-earned longevity increases in people with cystic fibrosis, early detection and intervention in preclinical CVD are critical. It is also time to rethink the classical high-fat cystic fibrosis diet in this context. The introduction of novel CFTR therapeutics offers substantial benefits to respiratory health and quality of life, but careful monitoring for cardiovascular risk factors is indicated. Together, people with cystic fibrosis and clinicians have shown that decades of targeted, preventative strategies can reduce the pulmonary and nutritional life-limiting manifestations of cystic fibrosis. Cardiovascular risk should be no different; the time for proactive prevention is now. ❐

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References

1. Silvestre, O. M. et al. *Am. Coll. Cardiol.* **72**, 1109–1122 (2018).
2. Teague, H. & Mehta, N. N. *Curr. Atheroscler. Rep.* **18**, 3 (2016).
3. Holman, R. L., Blanc, W. A. & Andersen, D. *Pediatrics* **24**, 34–39 (1959).
4. Gramegna, A. et al. *J. Cyst. Fibros.* https://doi.org/10.1016/j.jcf.2021.05.002 (2021).
5. Lai, S. et al. *J. Transl. Med.* **17**, 388 (2019).
6. Smith, C., Winn, A., Seddon, P. & Ranganathan, S. *J. Cyst. Fibros.* **11**, 154–157 (2012).
7. Hayden, H. S. et al. *Nat. Med.* **26**, 215–221 (2020).
8. Silverborn, M., Jeppsson, A., Martensson, G. & Nilsson, F. *J. Heart Lung Transplant* **24**, 1536–1543 (2005).
9. Petersen, M. C., Begnel, L., Wallendorf, M. & Litvin, M. *J. Cyst. Fibros.* https://doi.org/10.1016/j.jcf.2021.11.012 (2021).
10. Hadi, Y. B., Lakhani, D. A., Naqvi, S. F., Fatima, N. U. & Sarwari, A. R. *Respir. Med.* **188**, 106606 (2021).
11. Uramoto, H., Okada, T. & Okada, Y. *Cell Physiol. Biochem.* **30**, 1023–1038 (2012).
12. Li, Z. et al. *Biosci. Rep.* **37**, BSR20170680 (2017).
13. Nowak, J. K. et al. *J. Cyst. Fibros.* https://doi.org/10.1016/j.jcf.2021.06.010 (2021).
14. Poore, T. S., Taylor-Cousar, J. L. & Zemanick, E. T. *J. Cyst. Fibros.* https://doi.org/10.1016/j.jcf.2021.04.016 (2021).

Competing interests
The authors declare no competing interests.