The reduced ejection fraction is one of the most severe manifestations of cardiovascular disease. Since prior research showed that women with heart failure and reduced ejection fraction are less likely than men to die from heart failure and be hospitalized for it, the authors from the Netherlands investigated the sex-specific proteomic profiles in patients with heart failure and reduced ejection fraction, as well as the predictive value of repeatedly measured proteins. Understanding the pathophysiological mechanisms behind heart failure may be enhanced by the discovery of the sex-specific differences in cardiovascular protein profiles and their correlation with the likelihood of unfavorable consequences.

About the Study

A prospective cohort study comprised patients with stable heart failure and reduced ejection fraction. According to the guidelines of the European Society of Cardiology, the patients were older than 18 years and diagnosed with chronic heart failure more than three months before inclusion. Follow-up visits were scheduled every three months.

A clinical event committee determined the study endpoints. The primary endpoint comprised the composite of cardiovascular death, heart transplantation, left ventricular assist device implantation, and hospitalization for the management of acute or worsened heart failure. In patients with multiple endpoints, only the first was used for analysis.

Blood samples were collected at baseline and each follow-up visit. The authors selected all baseline samples and the two samples closest to the primary endpoint. They measured plasma proteins using the aptamer-based proteomic assay.

Results

The study included 382 patients, 104 (27.2%) women and 278 (72.8%) men, with similar mean ages (62 ± 13 *versus* 64 ± 13, respectively). Women had a significantly lower body

mass index and were more frequently current smokers than men. The ischemic etiology of heart failure was more frequent in men. Women had a lower prevalence of a history of myocardial infarction, percutaneous coronary intervention, and atrial fibrillation, and a lower median baseline level of high-sensitivity troponin T.

The primary endpoint reached 23/104 women and 91/278 men during a median follow-up of 25 months. The sexes did not differ in mean left ventricular ejection fraction.

During the follow-up, 1,070 blood samples were available. The levels of N-terminal-prohormone B-type natriuretic peptide and C-reactive protein were similar for both genders.

However, the baseline levels of some circulating proteins differed between the sexes. The analysis evaluated a set of 1,105 plasma proteins related to cardiovascular pathology. After correction for multiple testing, 55 proteins showed statistically significant differences based on sex. Women had higher levels of 34 proteins, such as heart-type fatty acid binding protein, adiponectin, osteoprotegerin, and galectin-3. Mean levels of 21 proteins were higher in men, including interleukin (IL)-1 receptor-like 1, myoglobin, and transforming growth factor β1.

According to the authors, five biological processes that dominated the circulating protein profiles in women were associated with extracellular matrix organization, positive regulation of the insulin-like growth factor receptor signaling pathway, and dendrite regeneration. Five processes that dominated the circulating protein profiles in men were related to the positive regulation of apoptotic processes, cell death, and the musculoskeletal system.

Although baseline cardiovascular protein levels differed between women and men, the predictive value of circulating proteins measured repeatedly did not differ between sexes except for endothelin-1 and somatostatin. The sex-specific levels of the circulating proteins endothelin-1 and somatostatin showed an association with adverse cardiovascular outcomes. Endothelin-1 levels were more strongly associated with the primary endpoint in men than in women. In contrast, somatostatin was positively associated with the primary endpoint in men and inversely associated with the primary endpoint in women. Endothelin-1 is considered a predictor of adverse clinical outcomes in heart failure and plays a key role in numerous aspects of cardiac physiology and pathology, such as hypertension, cardiac contractility, and cardiac remodeling. Somatostatin, also known as growth hormone-inhibiting hormone, has strong regulatory effects throughout the body, such as suppression of insulin-like growth factor I, growth hormone, and insulin.

The researchers emphasized the significant impact of heart failure on many tissues and organs throughout the body. Therefore, circulating protein levels in patients with heart failure reflect their production in non-cardiac tissues, either due to heart failure or other underlying comorbidities. Sex hormones or their receptors, extracellular matrix organization, apoptosis, and/or sex-specific differences in cardiovascular epigenetics could be the cause of the observed differences in proteomic profiles between sexes, but the exact mechanisms are not yet fully understood. However, the sex-specific differences in circulating proteins in patients with heart failure and reduced ejection fraction observed in this study do not necessarily reflect the sex-specific pathology. Still, they may also be a manifestation of physiologically based sex-specific differences.

Conclusion

This study evaluated a set of 1,105 plasma proteins to identify the sex-specific proteomic profiles and pathophysiological processes related to cardiovascular pathology in patients with heart failure with reduced ejection fraction. The results showed that women and men had different baseline levels of circulating proteins associated with cardiovascular pathology. Circulating proteins associated with extracellular matrix organization were overrepresented in women, while those reflecting apoptotic processes were overrepresented in men. Nevertheless, the predictive value of circulating proteins measured repeatedly did not differ between sexes, except for endothelin-1 and somatostatin.

This article was published in Biology of Sex Differences.

Journal Reference

de Bakker M *et al*. Sex-based differences in cardiovascular proteomic profiles and their associations with adverse outcomes in patients with chronic heart failure. Biol Sex Differ; 2023: 14, 29. https://doi.org/10.1186/s13293-023-00516-9