The authors from the Netherlands conducted a recent study that assessed gender differences in proteomic profile in patients with heart failure. They also examined the predictive value of repeatedly measured circulating proteins in patients with heart failure with a reduced ejection fraction (HfrEF). The findings revealed that the baseline levels of cardiovascular proteins differed between women and men. The predictive value of repeatedly measured circulating proteins did not differ between genders, except for endothelin-1 and somatostatin.

Multiple-marker assays have been developed to evaluate a wide range of circulating proteins, which represent various biological processes. Understanding the gender-specific profiles of cardiovascular proteins and their associations with the risk of adverse outcomes may help to improve our understanding of the pathophysiological processes.

The HFrEF is one of the most severe manifestations of cardiovascular disease. Women who have HFrEF are at a lower risk of hospitalization for heart failure (HF) and mortality than men.

About the study

A prospective cohort study comprised of 382 patients with stable HfrEF. According to European Society of Cardiology guidelines, the patients were older than 18 years and were diagnosed with chronic HF more than three months before inclusion. Follow-up visits were scheduled every 3 months.

The study endpoints were determined by a clinical event committee. 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 HF. Only the first endpoint was used for analysis in patients with multiple endpoints. The blood samples were collected at baseline and each follow-up visit. The authors have selected

all baseline samples and two samples that are closest to the primary endpoint.

1,070 samples were available during a median follow-up of 25 months. The aptamer-based proteomic assay was used to measure aptamers against 1105 circulating proteins that were previously associated with cardiovascular (patho)physiology.

In total, 104 (27.2%) women and 278 (72.8%) men were included, with similar mean age (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 HF was more frequent in men. Additionally, women had lower prevalence of the history of myocardial infarction, percutaneous coronary intervention and atrial fibrillation, and lower median baseline level of high-sensitivity troponin T. There were no clinically relevant differences between genders in mean left ventricular ejection fraction, N-terminal-pro hormone B-type natriuretic peptide or C-reactive protein.

The results showed that women and men have differences in baseline levels of circulating proteins. After correction for multiple testing, 55 proteins showed statistically significant differences based on gender. Women had higher levels of 34 proteins, including, heart-type fatty acid binding protein, adiponectin, osteoprotegerin, and galectin-3. Mean levels of 21 proteins were higher in men, including prostate-specific antigen, interleukin 1 receptor-like 1, myoglobin, and transforming growth factor β1.

The authors said that five biological processes that dominated the female circulating protein profile were associated with extracellular matrix organization, positive regulation of insulin-like growth factor receptor signaling pathway and dendrite regeneration. Five processes that dominated the male circulating protein profile were related to positive regulation of apoptotic processes and cell death and musculoskeletal movement.

During a median follow-up of 25 months, 23 women and 91 men reached the primary endpoint. Although baseline cardiovascular protein levels differed between women and men, the predictive value of repeatedly measured circulating proteins did not appear to differ. In the longitudinal associations with adverse cardiovascular outcome, a significant interaction was observed between gender and the circulating proteins endothelin-1 and somatostatin.

Endothelin-1 was found to be more strongly associated with the primary endpoint in men than in women. Endothelin-1 is considered to be a predictor of adverse clinical outcomes in HF and plays a key role in numerous aspects of cardiac physiology and pathology, such as hypertension, cardiac contractility, and cardiac remodeling.

The primary endpoint was positively associated with somatostatin in men, but it was inversely associated in women. 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.

Researchers noted that HF has a significant impact on many tissues and organs throughout the body. The levels of circulating proteins in patients with HF also reflect production in non-cardiac tissues, either as a consequence of the failing heart or other underlying comorbidities. Researchers speculated that observed differences between genders may be caused by the role of sex hormones or sex hormone receptors, the presence of extracellular matrix organization, and/or gender differences in cardiovascular epigenetics. However, the exact mechanisms are not completely understood. Moreover, the baseline gender-specific differences observed in this study do not necessarily reflect gender-specific pathophysiology. They may also be a manifestation of physiological gender-based differences.

In conclusion, this study evaluated a set of 1,105 plasma proteins in order to identify gender-specific differences in circulating protein levels and pathophysiological processes related to cardiovascular pathology in patients with heart failure with reduced ejection fraction. The findings showed that women and men had different baseline levels of circulating cardiovascular proteins. Circulating proteins associated with extracellular matrix organization were overrepresented in women, while circulating proteins reflecting apoptotic processes were overrepresented in men. Nevertheless, the predictive value of circulating proteins measured repeatedly did not differ between genders except for endothelin-1 and somatostatin.

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