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Gender Differences in the Response to Exercise in Heart Failure Associated with Metabolic Syndrome

Tóth ME, Sárközy M, Szűcs G, Dukay B, Hajdu P, Zvara Á, et al. Exercise training worsens cardiac performance in males but does not change ejection fraction and improves hypertrophy in females in a mouse model of metabolic syndrome. *Biol Sex Differ.* 2022;13:5. <https://doi.org/10.1186/s13293-022-00414-6>

There is a well-established association of obesity and metabolic syndrome with cardiovascular diseases such as atrial fibrillation, ischemic heart disease and heart failure. Conversely, the mechanisms underlying this relationship have not been clearly defined. Some of the most studied mechanisms include oxidative stress, inflammation, mitochondrial and endoplasmic reticulum dysfunction and programmed cell death, among others. Diverse studies in humans have shown specific sex differences in metabolic syndrome mechanisms. The effect of sex hormones in the regulation of lipid and carbohydrate metabolism is also well known. However, sex-based differences concerning the effects and mechanisms of physical training on heart failure associated with metabolic syndrome is scarcely understood.

In this work, Tóth et al. aimed to study sex differences in cardiovascular diseases related with metabolic syndrome and their response to regular physical exercise in an APOB-100 transgenic mice model (TG) fed

with a fat-rich diet, generating an adequate experimental model for the study of metabolic syndrome. Transgenic mice of both sexes were compared with wild-type (WT) mice fed with a standard diet. After seven months of physical exercise, the group of trained mice was compared with that of sedentary mice. Both male and female mice developed hypercholesterolemia and obesity, but only male mice showed insulin resistance. Metabolic parameters were not modified by training. Transgenic overfed male mice presented echocardiographic signs of mild heart failure and ventricular dilation, which worsened with physical exercise, reducing ejection fraction. Conversely, females with metabolic syndrome presented left ventricular hypertrophy without functional involvement, that reversed with exercise. Lastly, a higher expression of stress-response related genes was observed in exercise-trained male mice compared with females.

One of the interesting aspects of this work is the model of metabolic syndrome in mice, a species which is normally resistant to develop cardiovascular involvement in obesity. In this case, the authors could demonstrate differences in the behavior of males and females to physical exercise in a simulated context of global highly prevalent cardiometabolic conditions. These preclinical results could guide future prevention or cardiovascular complication management interventions in metabolic syndrome. Particularly, integral patient management with regular physical activity where the gender variable could play a role in decision-making.