

**Obesity and muscle loss in TIMP-2 knockout mice:
Understanding insulin in relation to sarcopenic obesity**

Holly M. Stradecki and Diane M. Jaworski.

Department of Anatomy & Neurobiology

Obesity increases the risks for cardiovascular disease, cancer, and type-2 diabetes, making the disorder one of the greatest financial burdens on the healthcare system. Sarcopenia, the age-related loss of muscle mass, is associated with frailty and falls. Given that skeletal muscle is the most insulin sensitive tissue and handles up to 95% of all insulin-mediated glucose usage, sarcopenic elderly often develop obesity. Leptin circulates in proportion to the amount of adipocytes and increases muscle insulin sensitivity, yet obesity is associated with insulin resistance and diabetes, which further weakens muscle. Identification of factors linking excess body fat and impaired insulin sensitivity in skeletal muscle has been difficult. Unexpectedly, the tissue inhibitor of metalloproteinase (TIMP) -2 knockout (KO) mouse gained weight on a normal chow diet and displayed some muscle defects. Extracellular matrix (ECM) remodeling occurs in physiological and pathological tissue remodeling. Therefore, we sought to understand the relationship between muscle loss and obesity as well as understand the contribution of ECM remodeling in this mouse model. We found male, but not female TIMP-2 KO mice show signs of sarcopenia. Mice of both genders gain more weight than wild-type mice when fed a standard chow diet and weight gain is exacerbated when fed a high fat diet, suggesting obesity alone is not the cause of muscle loss in male TIMP-2 knockout mice. Even though obese, TIMP-2 knockout mice of both genders display normal responses to glucose and insulin when fed the standard chow diet. However, when fed a high fat diet, male, but not female, TIMP-2 knockout mice developed glucose intolerance and insulin resistance, classic signs of metabolic syndrome. Taken together, TIMP-2 knockout mice may be obese, but as long as they consume a low fat diet they are spared from the metabolic complications of obesity.