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Azilsartan Ameliorates Skeletal Muscle Wasting in High Fat Diet (HFD)-induced Sarcopenic Obesity in Rats *via* Activating Akt Signalling Pathway

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ABSTRACT

An association between the loss of skeletal muscle mass and obesity in the geriatric population has been identified as a disease known as sarcopenic obesity. Therefore, therapeutic/preventive interventions are needed to ameliorate sarcopenia. The present study investigates the effect of azilsartan (AZL) on skeletal muscle loss in High-Fat Diet (HFD)-induced sarcopenic obese (SO) rats. Four- and fourteen-months male *Sprague Dawley* rats were used and randomized in control and azilsartan treatment. 14 months animals were fed with HFD for four months and labeled as HFD-fed SO rats. Young & old rats received 0.5% carboxymethyl cellulose as a vehicle/AZL (8 mg/kg, *per oral)* treatment for six weeks. Grip strength and body composition analysis were performed after the last dose of AZL. Serum and gastrocnemius (GN)muscles were collected after animal sacrifice. AZL treatment significantly increased lean muscle mass, grip strength, myofibrillar protein, and antioxidant (superoxide dismutase & nitric oxide) levels in SO rats. AZL also restored the muscle biomarkers (creatine kinase, myostatin & testosterone), and insulin levels. AZL improves cellular, and ultracellular muscle structure and prevents type I to type II myofiber transitions in SO rats. Further, immunohistochemistry results showed increased expressions of pAkt and reduced expression of MuRF-1 and TNF-α exhibiting that AZL intervention could decrease protein degradation in SO rats. In conclusion, present results showed that AZL significantly increased lean mass, and restored muscle biomarkers, and muscle architecture. Taken together, the aforementioned findings suggest that azilsartan could be a possible therapeutic approach to reduce muscle wasting in sarcopenic obesity.

1. Introduction

Sarcopenia is a musculoskeletal disease characterized by a decline in physical performance along with decreased muscle mass and muscle strength in old age (Kirk, et al., 2021). Sarcopenic obesity has recently been recognized as a significant factor contributing to the worsening of muscle condition due to the accumulation of visceral fat (Alalwan, 2020), excessive consumption of saturated fatty acid, (Lipina and Hundal, 2017) incessant inflammation, (Karanth, et al., 2021) and altered hormone levels (Choi, 2016). Moreover, the elderly, who tend to gain weight and lose muscle as they age, are particularly vulnerable to sarcopenic obesity (Roh and Choi, 2020). Recently, the European Association for the Study of Obesity (EASO) and the European Society for Clinical Nutrition and Metabolism (ESPEN) convened an international expert group to define sarcopenic obesity and come to a consensus on the myriad of confounding factors involved (Donini, et al., 2022, Shimizu, et al., 2022). Those factors include the chair stand test, knee extensor strength, and reference values calculated based on various population study variables such as age, gender, and ethnicity. Also, does not recommend the compulsory examination of gait speed in the diagnosis of sarcopenic obesity (Donini, et al., 2022). Mainly, sarcopenic obesity is diagnosed by altered skeletal muscle functional measures such

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