Supplementary Materials

Liver muscle bone axis in metabolic dysfunction-associated steatotic liver disease

Binhua Li[1,2,#], Yimeng Zhang[1,#], Can Zhou[1,#], Haixia Cao[1], Jing Zeng[1]

[1]Department of Gastroenterology, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200092, China.
[2]Second Department of Hepatology, The NO.2 People's Hospital of Lanzhou, Lanzhou 730030, Gansu, China.
[#]These authors contributed equally to this work.

Correspondence to: Dr. Haixia Cao, Dr. Jing Zeng, Department of Gastroenterology, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200092, China. E-mail: caohaixia@xinhuamed.com.cn; zengjing@xinhuamed.com.cn

Supplementary Table 1. Representative endocrine mediators involved in MASLD-related liver-muscle-bone crosstalk

Mediator	Main source and category	Principal target tissues	Relevance to MASLD and the liver-muscle-bone axis
FGF21[6,35,39]	Mainly a liver-derived hepatokine under metabolic stress; may also be exercise-responsive in skeletal muscle and adipose tissue	Liver, adipose tissue, skeletal muscle, central nervous system	Regulates fatty acid oxidation, energy expenditure, and glucose-lipid metabolism. Increased circulating levels in MASLD may reflect metabolic stress and possible FGF21 resistance rather than a uniformly protective response
Fetuin-A[39,40]	Liver-derived hepatokine	Skeletal muscle, adipose tissue, pancreas, immune cells	Associated with insulin resistance, impaired glucose metabolism, ectopic fat accumulation, and inflammatory activation, thereby linking hepatic metabolic stress with peripheral metabolic dysfunction
Selenoprotein P[39,40]	Liver-derived hepatokine	Skeletal muscle, pancreas, vascular tissue	Related to oxidative stress, impaired insulin signaling, reduced exercise responsiveness, and systemic metabolic dysfunction
Myostatin[41,42]	Predominantly skeletal muscle-derived myokine	Skeletal muscle, adipose tissue, liver	Acts as a negative regulator of muscle growth. Increased myostatin activity may promote muscle atrophy and contribute to insulin resistance, ectopic fat accumulation, and sarcopenia in chronic liver disease
Irisin[35,41,42]	Exercise-responsive myokine mainly produced by skeletal muscle	Adipose tissue, liver, skeletal muscle, bone	Promotes energy expenditure, mitochondrial adaptation, and exercise-related metabolic benefits. It may also participate in muscle-bone communication, although its clinical relevance in MASLD remains to be fully established
IL-6[34,35,37,38,41]	Context-dependent myokine and inflammatory cytokine; released by contracting muscle during exercise and by immune or adipose tissue during chronic inflammation	Liver, adipose tissue, skeletal muscle, immune system, bone	Acute exercise-induced IL-6 may support metabolic adaptation, whereas chronically elevated IL-6 may promote low-grade inflammation, insulin resistance, muscle catabolism, and abnormal bone remodeling
IL-15[35,41,42]	Myokine produced by skeletal	Skeletal muscle,	Involved in muscle metabolism, lipid oxidation, immune

	muscle; also expressed by immune cells	adipose tissue, immune system	regulation, and maintenance of lean mass. Its role in MASLD-related muscle dysfunction remains an area of ongoing investigation
BDNF[35,41,42]	Exercise-responsive neurotrophin produced mainly by the central nervous system and, to a lesser extent, skeletal muscle	Nervous system, skeletal muscle, metabolic tissues	Contributes to neuromuscular function, mitochondrial adaptation, and exercise-related metabolic improvement. Its direct role in MASLD remains less clearly defined
Adiponectin[36,39,40]	Adipose tissue-derived adipokine	Liver, skeletal muscle, vascular tissue, bone	Enhances insulin sensitivity, promotes fatty acid oxidation, and exerts anti-inflammatory effects. Reduced adiponectin levels in obesity and adipose dysfunction may aggravate hepatic steatosis, muscle insulin resistance, and metabolic inflammation. Its net effect on bone metabolism appears context-dependent
Leptin[40,43]	Adipose tissue-derived adipokine	Hypothalamus, liver, immune cells, hepatic stellate cells, bone	Regulates appetite and energy balance. In obesity, hyperleptinemia and leptin resistance may contribute to inflammation, hepatic stellate cell activation, and fibrogenic responses. Effects on bone remodeling may vary according to metabolic and hormonal context

BDNF: Brain-derived neurotrophic factor; FGF21: fibroblast growth factor 21; IL: interleukin; MASLD: metabolic dysfunction-associated steatotic liver disease.