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Editorial

High Fatty Liver Index and Fracture Risk: Clinical Implications

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See "Relationship between the High Fatty Liver Index and Risk of Fracture" by Min-Ji Kim, et al. on page 119, Vol. 17, No. 1, 2023

Osteoporotic fracture is one of the major health burdens in an aging society, leading to excess mortality and morbidity in older adults. From 2007 to 2011, the societal cost of osteoporotic fracture was estimated to increase annually from US $88.8 million in 2007 to US $149.3 million in 2011, and a steeper increase in health costs is expected according to rapid aging in South Korea.[1] Among Korean adults aged 50 or older, the cumulative incidence of subsequent fractures gradually increased over 4 years of follow-up once an osteoporotic fracture occurred, along with high crude fatality rates in the first 12 months after hip fracture (14.0% for women and 21.0% for men).[2] Despite recent advances in pharmacologic interventions including potent antiresorptive or anabolic agents such as denosumab or romosozumab, more tailored approach to reduce lifetime fracture risk at individual level remains unmet need to improve fracture prevention strategy, including the management of metabolic risk profiles.

Metabolic crosstalk between nonalcoholic fatty liver disease (NAFLD) and osteoporosis, as the most representative and prevalent metabolic diseases reflecting disrupted homeostasis in fat metabolism and the skeletal system, has been intensively investigated in prior literatures. However, the results remain controversial that some studies reported independent association of NAFLD with new onset osteoporosis, whereas some argued null association between NAFLD and bone mineral density.[3,4] Although common pathophysiologic links such as chronic inflammation and insulin resistance provide potential biological plausibility, the mechanical aspect of bone mass regulation makes interpretation of association between NAFLD and bone mineral density more complex that tendency toward obesity in individuals with NAFLD lead to constantly higher mechanical loading to axial bones, thereby preserving bone mass. Therefore, it would be important to study the fracture risk as clinical outcome in individuals with NAFLD for providing robust rationale to investigate crosstalk between NALFD and the skeletal system.

In this issue of *Gut and Liver*, Kim *et al.*[5] comprehensively assessed the association of biochemical indices of NAFLD (fatty liver index, FLI) with incident fracture risk during median 4.6 years of follow-up in a large Korean national claim database. Highest FLI quartile, calculated using triglyceride, body mass index, gamma-glutamyl transferase (GGT), and waist circumference, was associated with 23% increased risk of fracture compared to lowest quartile after adjustment for potential confounders. In subgroup analysis, the association between NALFD and elevated fracture risk remained robust in individuals with body mass index >25 kg/m^2, or those with normal blood pressure or fasting glucose level <126 mg/dL. As authors stated, these findings suggest that more clinical attention regarding fracture risk management may be warranted to individuals with high FLI score, with calls for future studies to elaborate mechanisms linking liver-bone axis.

Some clinical implications can be postulated from this finding. Although routine osteoporosis screening or fracture risk assessment in overall patients with NAFLD may not be supported by current evidences,[6] presence of risk factors such as prior fracture history, menopause, or concomitant glucocorticoid use can be utilized as clinical indications for bone density testing with fracture risk as-

sessment in patients with NAFLD. Severity of NAFLD assessed by biochemical indices, either by collective score or by separate components, may provide relevant information to set the threshold for indication of fracture risk assessment. Notably, in a recent study using the Korean national claim database, elevated serum GGT level, a component for FLI score, was associated with increased hip fracture risk in continuous fashion (17% increase per one log unit increment) in Korean postmenopausal women, which align well with the finding observed in Kim's study in this issue.[7] Considering the proposed association between elevated GGT and sarcopenia, as another musculoskeletal complication that linked to NAFLD, whether serum GGT testing can improve fracture risk prediction when added to established clinical risk factors is an interesting research topic that intersects liver-bone field.[8,9] Given the known negative impact of thiazolidinedione on bone mass and fracture risk in postmenopausal women, careful weighing of benefit and skeletal risk at individual level is warranted when commencing thiazolidinedione to improve NAFLD with biopsy-proven fibrosis. Receptor activator of nuclear factor-κB ligand (RANKL) is a key regulator of osteoclastogenesis. Humanized monoclonal RANKL antibody, denosumab, is now becoming a first-line bone active drug to reduce fracture risk with rapid gain of bone mass. Of note, RANKL is also reported to affect energy metabolism that RANKL blockade recovered hepatic insulin resistance and improved grip strength in rodent model.[10] Further evidences are awaited to test whether drug repurposing strategy using bone active drugs to treat NAFLD can be effective.

Taken together, accumulating evidences portend that deterioration of musculoskeletal function, represented by increased fracture risk in Kim's study, can be one of important clinical aspects in NAFLD that requires individualized management along with trend toward aging. Development of tailored strategy to effectively reduce fracture risk in patients with NAFLD, including targeting sarcopenia as one of potential therapeutic culprit, remains as clinical unmet need that calls further research.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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