A short Commentary on “Association between Non-Alcoholic Fatty Liver Disease and Bone Turnover Markers in Southwest China”

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As the most common chronic liver disease in worldwide, Non-Alcoholic Fatty Liver Disease (NAFLD) has become a research hotspot. Although the pathogenesis of NAFLD has not been fully elucidated, researchers have well recognized that NAFLD will affect multiple systems of the body rather than limited to the liver itself [1]. This is also consistent with the position of the liver as an important metabolic hub of the body. In addition, NAFLD is also considered to be the liver manifestation of the overall metabolic disorder of the body such as the Metabolic Syndrome (MetS) [2]. Therefore, discussing the metabolic changes of other organs or systems in the body during NAFLD, whether is directly induced by liver that as a pivotal organ of metabolism or just coexists with NAFLD in the “common soil” of the overall metabolic disorder of the body, will help to understand some relatively latent metabolic abnormalities.

The metabolic changes of bone during NAFLD have also attract the researchers’ attention. In fact, some scholars have noticed that NAFLD is related to Bone Mass Density (BMD) reduction [3]. Meanwhile, insulin resistance (IR), as the pathogenic mechanism of NAFLD, has also been found to be related to the skeletal system [4]. This makes scholars interested in exploring the correlation between NAFLD and bone metabolic disease. If the interaction indeed exists, it may be reflected by the changes of some biological molecules. In this case, certain bone turnover marker (BTM) should be good choice to explore the correlation between the two.

Furthermore, previous studies usually make qualitative diagnosis of NAFLD through abdominal color Doppler ultrasound which with artificial bias. In our study, the adipose deposition degree of NAFLD is quantitatively analyzed by Transient Elastography (TE). According to the two parameters from TE: fat attenuation parameter (FAP) and liver stiffness measurements (LSM), quantitative data of liver steatosis and stiffness can be detected, which has a good consistency with liver biopsy [5]. This will provide a better understanding of the correlation between NAFLD and BTMs.

Finally, we analyzed the physical examination data of 3353 subjects. Based on the actual situation of our study population, we selected 25-hydroxyvitamin D3 (25(OH)D3), osteocalcin, carboxy-terminal collagen crosslinks (CTX), amino terminal elongation peptide of total type 1 procollagen (P1NP) as BTMs to explore their changes in different FAP and LSM levels. The results revealed that with the increasing of FAP, the levels of 25(OH)D3 and osteocalcin decreased, the difference was statistically significant. No correlation was found between LSM and all the four BTMs. Logistic regression analysis revealed that FAP ≥ 244 dB/m was negatively correlated with 25(OH) D3 (in both males and females) and osteocalcin (only in males). No correlation was found between FAP ≥ 244 dB/m and P1NP or CTX.

Among the four BTMs we selected, 25(OH)D3 is a steroid derivative with a wide range of biological effects. As widely recognized, circulating 25(OH)D3 was mainly produced according to the hydroxylation of vitamin D by the CYP2R1 gene expression product 25-hydroxylase in the liver [6]. Decreased CYP2R1 gene expression and lower vitamin D levels were found in mice model of chronic liver disease [7]. This also makes us naturally speculate that the change of 25(OH)D3 in the presence of NAFLD may be one of the potential mechanisms of bone metabolic changes. It is also worth noting that in the subgroup analysis of our study, no differences in serum total calcium and phosphorus levels were found in different FAP levels, although 25(OH)D3 decreased with the increase of FAP. This seems to indicate that the body as an entity still gives priority to the balance of calcium and phosphorus levels in the circulation, and even partially sacrifices the mineral pool of the bone system and bone quality for this purpose.

Osteocalcin is produced by osteoblasts, and approximately 20% of synthesized osteocalcin is passes into the bloodstream and can be measured [8]. Our study suggests that osteocalcin levels are negatively correlated with FAP, but only in men. If this change of osteocalcin is caused by the functional change of osteoblasts, then it is an interesting question needs to be clarified that NAFLD through which mechanism to affect osteoblasts, and why this effect has gender differences.

In our study, no correlation was found between FAP and P1NP, CTX. As the products of collagen synthesis and degradation, P1NP and CTX are related to bone organic matter metabolism. These two BTMs have not been found to be related to FAP, suggesting that even
if NAFLD has effect on bone metabolism, it mainly regulates inorganic components, and seems have no significant effect on the metabolism of organic matter mainly composed of collagen in bone.

In our study, the change of BTMs level in NAFLD was mainly discussed. The inherent assumption here is to take NAFLD as the exposure factor. However, previous studies have found that some BTMs, such as osteocalcin, can act on the liver and improve the degree of NAFLD [9]. BTMs itself is a general term of a large class of biomolecules, and their sources, metabolism, distribution, and biological effects may vary greatly. For bones, the production of BTMs can be divided into “exogenous” and “endogenous”. 25(OH)D3 is a typical “exogenous” BTM and needs to be activated by the liver. Therefore, liver diseases can affect bone metabolism by changing 25(OH)D3. However, P1NP and CTX are mainly skeletal “endogenous” BTMs. If such BTMs are not mainly metabolized by the liver and not act on the liver, their changes only reflect the results of bone metabolism changes in NAFLD. And other “endogenous” BTMs such as osteocalcin is more complex, because osteocalcin itself has been found to have a regulatory effect on the liver. These kinds of BTMs make the relationship between NAFLD and bone is not only be considered as the one-way effect of NAFLD on bone, but also interact with each other, thus forming a more complex metabolic network.

In our study, we did not find the correlation between LSM and four BTMs, which may also be a limitation. The population in our study is based on the general health examination subjects, which can cover different levels of fat deposition, including people with severe elevated FAP level. However, the most LSM values of people with elevated LSM are just slightly increased. We speculate that under this degree of LSM difference, the liver is still functional enough as an entity that not to cause these four BTMs changes. Thus, to discuss the impact of liver stiffness on BTMs during NAFLD, more subjects with higher LSM levels and even cirrhosis need to be included for analysis.

In conclusion, ours and previous studies have shown that the levels of 25(OH)D3 and osteocalcin in the whole or part of the population during NAFLD are different from those in the non-NAFLD control population. In view of the actual situation of our study, only four BTMs such as 25(OH)D3 have been analyzed, however, more BTMs need to been discussed. Knowing about the changes of more BTMs in NAFLD may help to better understand the interaction between NAFLD and bone.

References

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