World Journal of Gastroenterology

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World J Gastroenterol 2024 February 21; 30(7): 636-643

DOI: 10.3748/wjg.v30.i7.636

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

EDITORIAL

Muscle strength and non-alcoholic fatty liver disease/metabolic-associated fatty liver disease

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Cigrovski Berkovic M, Croatia

Received: December 5, 2023
Peer-review started: December 5, 2023
First decision: December 7, 2023
Revised: December 12, 2023
Accepted: January 22, 2024
Article in press: January 22, 2024
Published online: February 21, 2024

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Abstract

This editorial comments on an article published in a recent issue of *World Journal of Gastroenterology,* entitled "Association of low muscle strength with metabolic dysfunction-associated fatty liver disease: A nationwide study". We focused on the association between muscle strength and the incidence of non-alcoholic fatty liver disease (NAFLD) and metabolic-associated fatty liver disease (MAFLD), as well as the mechanisms underlying the correlation and related clinical applications. NAFLD, which is now redefined as MAFLD, is one of the most common chronic liver diseases globally with an increasing prevalence and is characterized by malnutrition, which may contribute to decreased muscle strength. Reduction of muscle strength reportedly has a pathogenesis similar to that of NAFLD/MAFLD, including insulin resistance, inflammation, sedentary behavior, as well as insufficient vitamin D. Multiple studies have focused on the relationship between sarcopenia or muscle strength and NAFLD. However, studies investigating the relationship between muscle strength and MAFLD are limited. Owing to the shortage of specific medications for NAFLD/MAFLD treatment, early detection is essential. Furthermore, the relationship between muscle strength and NAFLD/MAFLD suggests that improvements in muscle strength may have an impact on disease prevention and may provide novel insights into treatments including dietary therapy, as well as tailored physical activity.

Key Words: Muscle strength; Non-alcoholic fatty liver disease; Metabolic-associated fatty liver disease; Sarcopenia; Insulin resistance; Inflammation

Core Tip: The relationship between muscle strength and the incidence of non-alcoholic fatty liver disease (NAFLD) and metabolic-associated fatty liver disease (MAFLD), as well as the mechanisms underlying the correlation and related clinical applications were discussed. Muscle strength may play an imperative role in the incidence and development of NAFLD/MAFLD and interventions to improve muscle strength in the management of NAFLD/MAFLD may provide novel insights into the treatment of these diseases.

Citation: Hao XY, Zhang K, Huang XY, Yang F, Sun SY. Muscle strength and non-alcoholic fatty liver disease/metabolic-associated fatty liver disease. *World J Gastroenterol* 2024; 30(7): 636-643
URL: https://www.wjgnet.com/1007-9327/full/v30/i7/636.htm
DOI: https://dx.doi.org/10.3748/wjg.v30.i7.636

INTRODUCTION

As an imperative component of human health and a crucial predictor of physical function, muscle strength has drawn great interest in the areas of disease prediction and treatment[1,2]. Non-alcoholic fatty liver disease (NAFLD), recently renamed metabolic-associated fatty liver disease (MAFLD), with liver biopsy as the gold standard for diagnosis, is a common chronic liver disease, and its prevalence is still increasing, representing a global healthcare burden[3,4]. NAFLD/ MAFLD is characterized by malnutrition, which may contribute to decreased muscle mass, strength, and sarcopenia[5,6]. NAFLD encompasses a broad disease spectrum ranging from non-alcoholic fatty liver to cirrhosis, which is a representative cause of sarcopenia due to protein and energy metabolic disorders[7,8].

Sarcopenia is now defined as low muscle strength combined with low muscle quantity or quality with or without poor physical performance after revision by the European Working Group on Sarcopenia in Older People 2[9]. However, the measurements for diagnosis of sarcopenia differs according to clinical practice and research. In addition, some studies have utilized the previous definition of sarcopenia, which focused only on decreased muscle mass and not on low muscle strength. Multiple studies have focused on the association between sarcopenia or muscle strength and NAFLD; however, studies on the relationship between muscle strength and MAFLD are rare. As the primary parameter for sarcopenia in the updated definition, decreased muscle strength has also been suggested as a better predictor of mortality and poor disease outcomes than has muscle mass in previous studies[9-11]. Thus, further exploration of the association between low muscle strength and NAFLD/MAFLD is necessary. Muscle strength is usually measured using grip strength, which is noninvasive, low-cost, uncomplicated, and has been validated reliably in research and clinical practice[12]. Lower limb strength can also be measured when grip strength is not available[13].

MUSCLE STRENGTH AND NAFLD/MAFLD

In a recent issue of *World Journal of Gastroenterology*, Lee *et al*[14] published an absorbing article titled "Association of low muscle strength with metabolic dysfunction-associated fatty liver disease: A nationwide study". This study verified a significant relationship between muscle strength and MAFLD in the general Korean population. The present cross-sectional study examined 31649 participants aged ≥ 19 years who took part in the Korea National Health and Nutrition Examination Survey between 2015 and 2018. Of the enrolled participants, 29.3% had MAFLD diagnosed using the hepatic steatosis index and the presence of metabolic risk factors. The muscle strength of the participants was defined by relative handgrip strength and divided into quartiles. Multivariate logistic regression analysis revealed that the prevalence of MAFLD was higher in the lower muscle strength quartiles. The lowest quartile exhibited a 3.12-fold increased risk of MAFLD compared to that in the highest quartile. A significantly elevated odds ratio for MAFLD was also observed in the lower muscle strength quartiles in a dose-dependent manner. These associations persisted across all subgroups, including age, obesity, and diabetes mellitus. Patients with MAFLD in the highest quartile also had increased risks of severe liver fibrosis compared to those in the other quartiles. The study indicated that decreased muscle strength was related to a dose-dependent higher risk of MAFLD as well as to a high probability of liver fibrosis in participants with MAFLD.

Studies that have explored the association between muscle strength and NAFLD are presented in Table 1. The relationship between NAFLD and low muscle strength was demonstrated in a cross-sectional study by Gan *et al*[15]. The occurrence of NAFLD was higher in the sarcopenic state, and this risk was further elevated if obesity was present. The results also showed that low muscle strength, measured using weight-adjusted handgrip strength, was positively, independently, and significantly associated with NAFLD. An association between low muscle strength and increased incidence of NAFLD has been detected in the Korean population[16-19]. Similar findings have been validated in the Chinese population and HIV-infected men in Italy, as well as in the male patients diagnosed with type 2 diabetes mellitus [20-23]. Further, low muscle strength was related to a higher incidence of severe NAFLD in a prospective study using data derived from the UK Biobank[24]. These results indicated that lower muscle strength was significantly associated with an increased incidence of severe NAFLD. In another study by Kang *et al*[25], decreased muscle strength was

Table 1 Studies fucus on the relationship between muscle strength and non-alcoholic fatty liver disease

Ref.	Study design	Subjects	Sample size and gender [female; *n* (%)]	Mean age (yr)	Strength position/measures	Outcome
Gan *et al*[15], 2020	Cross-sectional study	General adults in China	3536 (71.3)	51.72 for participants without NAFLD/55.2 for participants with NAFLD	Handgrip strength (kg)/electronic hand dynamometer	Incidence of NAFLD
Lee *et al*[16], 2018	Cross-sectional study	General adults in Korea	8001 (55.5)	49.9	Handgrip strength (kg)/digital grip strength dynamometer	Incidence of NAFLD
Kim *et al*[17], 2019	Cross-sectional study	Men aged ≥ 50 yr and postmenopausal women in Korea	4103 (53.8)	61.9 for men without NAFLD/59.5 for men with NAFLD/61.8 for women without NAFLD/62 for women with NAFLD	Handgrip strength (kg)/digital grip strength dynamometer	Incidence of NAFLD
Cho *et al*[18], 2021	Cross-sectional study	Middle-aged adults in Korea	5272 (68.2)	57.1	Handgrip strength (kg)/digital grip strength dynamometer	Incidence of NAFLD
Lee *et al*[19], 2022	Cross-sectional study	General adults in Korea	19852 (62.5)	45.8 for men/48.3 for women	Handgrip strength (kg)/digital grip strength dynamometer	Incidence of NAFLD
Debroy *et al*[20], 2019	Cross-sectional study	Adults living with HIV and receiving treatment in Italy	169 (0)	56.8	Handgrip strength (kg)/handheld dynamometer	Incidence of NAFLD
Meng *et al*[21], 2016	Cross-sectional study	General adults in China	20957(49)	41.2	Handgrip strength (kg)/electronic hand-grip dynamometer	Incidence of NAFLD
Bulur *et al*[22], 2023	Cross-sectional study	Middle-aged male patients diagnosed with type 2 diabetes mellitus	145 (0)	55.2	hand muscle strength (kg)/hydraulic dynamometer	Incidence of NAFLD
Wang *et al*[23], 2021	Cross-sectional study	Senior hospital staff in China	578 (84.1)	72.9 for men without NAFLD/68.9 for men with NAFLD/62.9 for women without NAFLD/67.5 for women with NAFLD	Handgrip strength (kg)/hydraulic hand dynamometer	Incidence of NAFLD
Petermann-Rocha *et al*[24], 2022	prospective study	General adults in Scotland, England and Wales	333295 (55)	56.6	Handgrip strength (kg)/hydraulic hand dynamometer	Incidence of severe NAFLD
Kang *et al*[25], 2020	Cross-sectional study	General adults in Korea	13502 (57.6)	45.6	Handgrip strength (kg)/digital grip strength dynamometer	Incidence and severity of NAFLD
Park *et al*[26], 2020	Cross-sectional study	General adults in the USA	3922 (58.1)	45 for men/46.9 for women	Handgrip strength (kg)/digital grip strength dynamometer	Incidence and severity of NAFLD
Zhao *et al*[27], 2023	Cross-sectional study	General adults in the USA	8888 (50.43)	46.07	Handgrip strength (kg)/digital grip strength dynamometer	Incidence and severity of NAFLD
Kim *et al*[28], 2023	Cross-sectional study	General adults with NAFLD in the USA	4655 (46.9)	48	Handgrip strength (kg)/digital grip strength dynamometer	All-cause and cause-specific mortality in NAFLD
Charatcharoenwitthaya *et al*[29], 2022	Observational study	General adults with NAFLD in the Thailand	7083 (69.4)	49.3	Handgrip strength (kg)/digital dynamometer	All-cause mortality in NAFLD

NAFLD: Non-alcoholic fatty liver disease.

independently related to the incidence and progression of NAFLD in a Korean population. Additionally, grip strength was inversely associated with NAFLD severity in a United States population[26,27]. Furthermore, higher muscle strength was independently related to lower all-cause and cardiovascular mortality after full adjustment in patients with NAFLD in a United States population[28]. Muscle strength was independently associated with long-term all-cause mortality in participants with NAFLD in a study conducted in Thailand[29]. However, few studies have compared the predictive value of muscle strength in NAFLD and MAFLD.

POTENTIAL MECHANISM FOR THE RELATIONSHIP BETWEEN MUSCLE STRENGTH AND NAFLD/MAFLD

The potential mechanisms that may explain the relationship between muscle strength, NAFLD/MAFLD, and cirrhosis have yet to be explored. Insulin resistance may play a crucial role in the inverse relationship between muscle strength and NAFLD/MAFLD. Skeletal muscle is the primary target organ of insulin-stimulated glucose disposal; therefore, a reduction in muscle strength may exacerbate insulin resistance, which is a crucial pathogenic component of NAFLD/MAFLD, through hepatic fat accumulation, inflammation, and energy metabolism alteration[30-32]. Insulin resistance in turn aggravates proteolysis and itself leads to muscle depletion[33]. Several inflammatory mechanisms related to NAFLD, such as cirrhosis, have been identified[34,35]. As a characteristic of NAFLD, dysfunction of adipocyte lipolysis is suggested to lead to ectopic fat accumulation in hepatic parenchyma as well as skeletal muscle[36,37]. Higher levels of inflammatory markers, including C-reactive protein, interleukin (IL)-6, and tumor necrosis factor-α, observed in populations with lower muscle strength indicated that decreased muscle strength may be associated with NAFLD/MAFLD and cirrhosis based on inflammation[38]. Elevated levels of proinflammatory cytokines may result in muscle degradation by reducing the muscle response to insulin and insulin-like growth factor-1[39]. Alterations in myokines (such as irisin, IL-6, myostatin, and adiponectin) secreted by skeletal muscle may be involved in NAFLD/MAFLD development through their influence on hepatic fat accumulation[40]. A previous study found that decreased muscle strength was related to lower vitamin D levels and that vitamin D supplementation contributed to muscle strength preservation[41,42]. Epidemiological data also support that vitamin D is associated with the incidence of NAFLD and that the vitamin D/vitamin D receptor axis is involved in the modulation of inflammatory and metabolic pathways related to MAFLD[43,44]. Decreased muscle strength is related to physical disability and functional decline as well as sedentary behavior, which is related to the development of NAFLD/MAFLD[45-47].

CLINICAL IMPLICATION

Recovery from decreased muscle strength may decrease complications and improve survival in individuals with fatty liver disease[10,48]. Because sarcopenia is related to nutritional status, dietary therapy based on optimal nutritional intake has been suggested for its treatment in fatty liver disease and cirrhosis[49]. Supplementation with branched-chain amino acids and adequate energy in conjunction with a protein-enriched dietary intake has been recommended for individuals with liver cirrhosis[50]. As a non-pharmacological and innovative strategy, proper physical activity can be effective in recovering lost muscle strength. A previous study illustrated that progressive resistance training could increase muscle strength and improve general performance, including functional exercise capacity, mental health, and body composition, in patients with cirrhosis[51]. Furthermore, implementation of tailored physical activity may improve outcomes in patients awaiting liver transplantation[52]. A recent meta-analysis indicated that combining protein supplementation with resistance training is advisable for optimizing muscle strength[53]. The findings of a cross-sectional study suggested that adherence to an anti-inflammatory nutrient pattern, characterized by a high intake of polyunsaturated fat, monounsaturated fat, copper, vitamin E, and omega-3 fatty acids was associated with reduced odds of low muscle strength, which indicated that anti-inflammatory pattern might be a therapeutic approach for decreased muscle strength[54]. Despite the beneficial impact of physical activity on muscle strength, specific exercise training guidelines for individuals with fatty liver disease and cirrhosis are lacking in terms of the amount, intensity, and forms of exercise in clinical practice[55,56]. Electrical stimulation has also emerged as a popular modality for enhancing muscle strength among athletes and fitness enthusiasts; however, the lack of standardized protocols pertaining to its specific implementation remains a challenge[57].

The correlation between muscle strength and NAFLD/MAFLD might provide a fresh perspective for treatment owing to the lack of specific medications[58]. Although there are no specific pharmacotherapeutic interventions for reduced muscle strength to date, multiple efforts have already been made, including a variety of clinical trials that focused on pharmacological interventions for sarcopenia[59,60]. Several drugs have been investigated for their ability to augment muscle strength based on different molecular targets. Bimagrumab, a fully human monoclonal antibody targeting the MSTN-ActRII pathway, was found to be useful for increasing muscle strength in patients with sarcopenia in phase 2 clinical trials[61]. However, in a clinical trial performed by Rooks *et al*[62], bimagrumab demonstrated no positive effect on muscle strength. Medications targeting the renin–angiotensin system, such as inhibitors of angiotensin-converting enzyme, have also been found to influence the decline in muscle strength[63]. The efficacy of dipeptidyl peptidase-4 inhibitors for enhancing muscle strength in geriatric patients with type 2 diabetes mellitus was investigated in a recent retrospective cohort study[64]. Furthermore, several studies have demonstrated the potential benefits of testosterone for improving muscle strength. The most recent Clinical Practice Guideline by the Endocrine Society suggested that

testosterone treatment can enhance muscle strength in men with hypogonadism[65]. A meta-analysis also found that intramuscular testosterone replacement therapy is effective in improving muscle strength in middle-aged and older men [66]. In addition, owing to their beneficial effects on muscle strength, exercise mimetics, which can induce energy expenditure without changes in activity, have been recognized as a potential therapeutic strategy[67].

CONCLUSION

In summary, muscle strength has an imperative function in the incidence of NAFLD/MAFLD and may serve as a potential predictor for early diagnosis, as well as a better means of evaluating NAFLD/MAFLD. Interventions based on muscle strength may provide novel insights into the treatment of NAFLD/MAFLD.

FOOTNOTES

Author contributions: Sun SY and Zhang K were involved in the study conception and design; Hao XY, Zhang K, Huang XY and Yang F wrote the manuscript; Sun SY performed critical revision of the article for important intellectual content; all authors approved the final version of the article.

Supported by National Natural Science Foundation of China, No. 82000625; and the Doctoral Scientific Research Foundation of Liaoning Province, No. 2020-BS-109.

Conflict-of-interest statement: The authors declare that there are no conflicts of interest.

Country/Territory of origin: China

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S-Editor: Lin C
L-Editor: A
P-Editor: Chen YX

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