Journal of Health, Sports, and Kinesiology, 2021, 2(2), 35-39

Research Critique **Open Access**

Article History:
Received 10 April 2021
Accepted 26 April 2021
Published 1 August 2021
Available online 30 July 2021
https://doi.org/10.47544/johsk.2021.2.2.35

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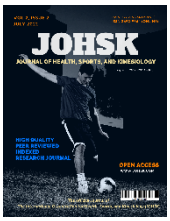

Relationship Between Nonalcoholic Fatty Liver Disease and Low Skeletal Muscle Mass in Obese Youth

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Keywords: NAFLD, NASH, childhood obesity, skeletal muscle mass

Abstract
Previous studies in adults have found a correlation between nonalcoholic fatty liver disease (NAFLD) and sarcopenia. The present study evaluated the relationship between NFALD and skeletal muscle mass in overweight/obese youth. A total of 234 children and adolescents (age 8-16) was stratified into tertiles based on relative muscle mass (RMM). Total, regional lean body mass, and total fat mass were obtained by dual-energy X-ray absorptiometry. RMM was defined as the percent of muscle mass (kg) relative to the sum of muscle and fat mass (kg). NAFLD was diagnosed via ultrasononography and a subset of participants with NAFLD (n=40) underwent a liver biopsy. The lowest tertile had a significantly higher risk for obesity, dyslipidemia, insulin resistance, metabolic syndrome, NAFLD, and nonalcoholic steatohepatitis (NASH). The present study demonstrated an association between low muscle mass, NAFLD, and NASH in overweight/obese youth. Despite the strong scientific merits of the present study, a lack of race/ethnic description could be a major critique as different ethnic background (specifically in the minorities) may be disproportionately impacted by fat distribution and relative muscle mass. Even though there is a clear relationship between sarcopenia and NAFLD in the elderly, this association may not stem from the same origin in the pediatric population. Lastly, but not least, future studies should evaluate NAFLD in obese youth with varying degrees of metabolic disorders (i.e., metabolic syndrome).

Introduction
NAFLD is currently one of the most prominent chronic diseases in the world, affecting 30% of adults in the U.S. and 60-70% of adults who are obese and diabetic (Farzanegi et al., 2019). NAFLD encompasses a multitude of liver complications including simple steatosis, NASH, and/or cirrhosis. NAFLD is diagnosed if accumulated triglycerides (TG) within hepatocytes exceeds 5% of the liver weight (Kneeman et al., 2012). Common risk factors for developing NAFLD include obesity, type 2 diabetes, hyperlipidemia, and hypertension (Pacifico et al., 2020).

Due to its nature of pathophysiology, NAFLD is often implicated with metabolic syndrome. Similar risk factors between the two disorder conditions are abdominal obesity, increased blood pressure, high levels of TG, insulin resistance, and glucose abnormalities (Pacifico et al., 2020). A significant overlap between these two suggests that patients diagnosed with NAFLD should be particularly weary of cardiovascular disease. The combination of a healthy diet and exercise routine has shown to be effective at preventing/ameliorating the unwanted effects of NAFLD on cardiometabolic health (Farzanegi et al., 2019). Previous studies have demonstrated a relationship between NAFLD and low skeletal muscle mass in the adult/geriatric population. However, there is a lack of research on the potential relationship between NAFLD characteristics and skeletal muscle mass profile in the pediatric population.

It is essential to study metabolic disorders such as NAFLD in children and adolescents (especially with obesity) in order to reduce the prevalence of disease and implement healthy lifestyle habits that will last through adulthood. To the best of our knowledge, the present study entitled "Nonalcoholic Fatty Liver Disease Is Associated with Low Skeletal Muscle Mass in Overweight/Obese Youths" is the first study to assess the relationship between skeletal muscle mass and NAFLD in a pediatric population (Pacifico et al., 2020).

Purpose

The purpose of the present study was to determine if there was a correlation between low skeletal muscle mass and NAFLD in overweight/obese children and adolescents.

Methods

A total of 234 children and adolescents (age 6-18 years) was recruited from the Clinics of the Department of Pediatrics (Sapienza University of Rome) for this study. Inclusion criteria was overweight/obese classification (body mass index [BMI] >85th percentile for age and sex), nondiabetic, free of chronic diseases and conditions that influence body composition. The pubertal status was measured by Tanner stage. Following an overnight fast, blood samples were collected to determine plasma glucose, insulin, total cholesterol, high-density lipoprotein cholesterol (HDL-C), TG, alanine aminotransferase (ALT), and aspartate aminotransferase (AST). Insulin resistance was assessed by the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) using fasting insulin and fasting glucose concentrations.

An ultrasonography of the liver was used to diagnose NAFLD. Diagnosis of NAFLD was based upon liver echogenicity exceeding that of the renal cortex and spleen, attenuation of ultrasound wave, loss of definition of the diaphragm, and poor delineation of the intrahepatic architecture. RMM was defined as the percent of muscle mass relative to the sum of muscle and fat mass. Appendicular skeletal muscle mass (ASM) was defined as the sum of the muscle mass in the four limbs (kg) and expressed as percent of body weight [ASM/weight (kg) x 100]. Following evaluation, a subset of obese participants (n=40) diagnosed with NAFLD underwent a percutaneous needle liver biopsy in order to screen for NASH.

Researchers examined the liver sample for liver steatosis, lobular/portal inflammation, hepatocyte ballooning, and fibrosis. Patients were diagnosed with NASH upon the presence of steatosis with necroinflammation and hepatocyte ballooning. The subjects were split into three tertiles based on RMM.

Results

The tertile with the lowest RMM had the greatest BMI, BMI standard deviation (BMI-SDS), waist circumference (WC), total body fat mass as well as the highest TG/HDL-C ratio, fasting insulin, and HOMA-IR (Table 1), leading the highest prevalence of metabolic syndrome and NAFLD. Under standardized age, sex, and Tanner stage, children in the lowest tertile of RMM had the highest risk for NAFLD (OR=2.80, 95% CI=1.57-5.02) compared with those in the other two tertiles. This association mostly persisted even after adjusting for potential confounders including central obesity, elevated blood pressure, elevated TG, low HDL-C, and insulin resistance. In the subset of participants that underwent a liver biopsy, 24 children tested positive for NASH, while 16 tested negative. Children with NASH showed significantly lower RMM [mean, 55.7 (SD, 6.0) vs. 63.4 (6.0) %; P<0.0001] and lower ASM/weight index [mean, 25.6 (SD, 2.8) vs. 28.6 (2.9) %; P=0.006].

NASH was most common in the lowest tertile of RMM [70.8 (95% CI, 61.8-79.8) % vs. 29.2 (20.2-38.2) %; P<0.001] as well as in the lowest tertile of ASM/weight index compared to those in the other two tertiles [62.5 (95% CI, 47.5-77.5) % vs. 37.5 (22.5-52.5) %; P<0.003, respectively]. After controlling for age, sex and Tanner

stage; the risk of NAFLD (OR=2.99, 95% CI =1.41-6.31) in the lowest tertile of ASM/weight index was significantly higher compared to that in the other two tertiles. Overall, RMM appeared to be negatively correlated with WC, diastolic BP, ALT, TG, TG/HDL-C ratio, insulin, and HOMA-IR.

Table 1. Characteristics of Study Population According to Tertiles of RMM[a] .
(Adapted from Table 1 of original research study [Pacifico et al. Frontiers in Pediatrics, 8; 1–8]).

	Relative Muscle Mass (RMM)			
	Tertile I	**Tertile II**	**Tertile III**	***P***
Number of subjects	78	75	81	
Age, years	11.3 (2.3)	11.5 (2.8)	12.5 (3.0)	0.06
Male sex, n (%)	38 (48.7)	33 (44.0)	61 (75.3)	0.001
Prepubertal Status	15 (19.2)	16 (21.3)	14 (17.2)	0.26
Weight, kg	65.0 (21.0)	59.3 (22.1)	64.1 (21.1)	0.21
Height, cm	149.7 (14.4)	151.7 (17.4)	158.9 (18.0)	0.01
BMI (kg/m^2)	28.3 (4.5)	24.7 (3.7)	24.6 (3.3)	<0.0001
BMI-SD score	2.13 (0.40)	1.70 (0.39)	1.60 (0.39)	<0.0001
Waist circumference, cm	91.2 (13.2)	84.8 (14.0)	84.6 (12.0)	0.002
Systolic BP, mmHg	111 (11)	111 (9)	112 (13)	0.81
Diastolic BP, mmHg	69 (9)	68 (8)	69 (9)	0.82
Total cholesterol, mg/dL	170 (39)	177 (50)	163 (41)	0.19
HDL-C, mg/dL	46 (13)	47 (12)	49 (10)	0.17
Triglycerides, mg/dL	97(72-141)	91 (65-128)	76 (52-123)	0.031
TG/HDL-C ratio	2.1 (1.3-3.6)	1.9 (1.2-3.3)	1.6 (0.9-2.8)	0.029
AST, U/L	25 (20-34)	25 (20-30)	23 (19-29)	0.22
ALT, U/L	25 (17-47)	22 (15-35)	20 (15-32)	0.15
Glucose, mg/dL	4.8 (0.8)	4.8 (0.45)	4.8 (0.39)	0.84
Insulin, μU/mL	18 (12-24)	14 (9-19)	13 (9-18)	0.004
HOMA-IR	3.7 (2.5-4.8)	2.8 (1.9-3.9)	2.8 (2.0-4.0)	0.015
Total body fat mass, kg	28.0 (10.0)	22.8 (9.0)	19.0 (5.9)	<0.0001
Total lean body mass, kg	31.4 (9.6)	32.5 (12.7)	39.6 (14.6)	<0.0001
RMM, %	53.0 (3.3)	58.9 (1.5)	66.9 (4.8)	<0.0001
ASM, kg	15.1 (4.36)	15.5 (7.0)	20.7 (7.94)	<0.0001
ASM/weight index, %	24.5 (1.73)	26.2 (2.86)	30.8 (7.42)	<0.0001
ASM/ht2	6.7 (1.0)	6.4 (1.6)	7.6 (2.0)	0.001
NAFLD, n (%)	43 (55.2)	25 (33.3)	27 (33.3)	0.006

RMM, relative muscle mass; BMI, body mass index; BMI-SDS, BMI-SD score; BP, blood pressure; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HOMA-IR, homeostasis model assessment of insulin resistance; ASM, appendicular skeletal muscle mass.
[a]Tertile I, RMM: < 56.72; tertile II, RMM: 56.72–61.99; tertile III, RMM: > 61.99.
Results are expressed as n (%), mean (SD) or median (interquartile range)

Conclusion

This study concluded that overweight/obese youth with lower muscle mass have a greater risk of NAFLD compared to those with higher muscle mass, and this inverse relationship between NAFLD and muscle mass in children and adolescents is independent from anthropometric/metabolic variables. In addition, overweight/obese youth with lower muscle mass demonstrate a greater prevalence of cardiometabolic risk factors (e.g., central obesity, dyslipidemia, and insulin resistance) and are at a higher risk for metabolic syndrome.

Critique

The present study found that overweight/obese youth with lower muscle mass have a greater risk of NAFLD/NASH and other metabolic diseases compared to those with higher muscle mass. The researchers assessed the muscle mass of participants by using both RMM and ASM, as opposed to only using a single metric of assessing muscle mass. Using multiple metrics of muscle mass is ideal because it reduces the likelihood of lurking variables that may arise from disproportionate skeletal muscle distribution between participants.

Although the researchers standardized the data based on age, sex, and tanner stage, potential ethnic variations of participants Were not considered. Ethnicity likely plays a very influential role as it can impact both fat distribution (stemming from unique genetics, socioeconomic status, diet, etc.) (Robinson et al., 2012) and RMM (Silva et al., 2009).

Moreover, considering that NAFLD and sarcopenia is often associated with metabolic syndrome, it may be useful to study metabolic syndrome-related variables aside from obesity and insulin resistance such as inflammation (i.e., C-reactive protein) as well as markers of muscle breakdown (i.e., creatine kinase). The present study alludes to previous studies that linked sarcopenia and NAFLD in the adult/geriatric populations (Kim et al., 2017). Indeed, the mechanism by which NAFLD and sarcopenia are linked may differ between children and adults. In adults/elderly, sarcopenia is largely attributed to the progressive loss of motor neurons over time, resulting in a preferential loss of type II muscle fibers (Larsson et al., 2019). Type II muscle fiber loss in aging adults has been linked to hormonal changes (i.e., testosterone) and a reduction of available satellite cells (Walston, 2012).

In addition, environmental factors (i.e., poor diet and/or poor exercise), chronic inflammatory diseases (i.e., rheumatoid arthritis), and mitochondrial abnormalities (i.e., mutations in mitochondrial DNA) can further degrade muscle mass in adults (Kvorning et al., 2015; Walston, 2012). At any rate, the relationship between sarcopenia and NAFLD in pediatrics may arise from overlapping factors as adults. In both children and adults, malnutrition and a sedentary lifestyle contribute to the development of sarcopenia (Gilligan et al., 2020). However, sarcopenia in children may be more influenced by these factors in particular because children appear to be less prone to declining anabolic hormones/mitochondrial dysfunctions that parallel aging and have usually been exposed to environmental stresses for a much shorter period of time compared to adults.

Therefore, studying the effects of an intervention of a healthy diet and/or exercise program in a sample of pediatric patients with prior substandard diets/physical activity levels may provide more insight on the role of diet/exercise in the relationship between childhood sarcopenia and NAFLD. Phenotyping of both type I and type II muscle fibers may lead to novel findings on the potentially unique mechanisms of pediatric sarcopenia (compared to adults). Finally, future studies should try to obtain a larger and more diverse sample and evaluate a wider range of variables.

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