Editorial

Body fat distribution: a crucial target for intervention in nonalcoholic fatty liver disease and fibrosis

Karn Wijarnpreecha[1,2]^, Aijaz Ahmed[3]^, Donghee Kim[3]^

[1]Division of Gastroenterology and Hepatology, Department of Medicine, University of Arizona College of Medicine, Phoenix, AZ, USA; [2]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Banner University Medical Center, Phoenix, AZ, USA; [3]Division of Gastroenterology and Hepatology, Stanford University School of Medicine, Stanford, CA, USA

Correspondence to: Donghee Kim, MD, PhD. Division of Gastroenterology and Hepatology, Stanford University School of Medicine, 300 Pasteur Drive, Stanford, CA 94304, USA. Email: messmd@chol.com; dhkimmd@stanford.edu.

Comment on: Ciardullo S, Oltolini A, Cannistraci R, *et al.* Sex-related association of nonalcoholic fatty liver disease and liver fibrosis with body fat distribution in the general US population. Am J Clin Nutr 2022;115:1528-34.

Submitted Aug 15, 2022. Accepted for publication Sep 05, 2022.
doi: 10.21037/hbsn-22-366
View this article at: https://dx.doi.org/10.21037/hbsn-22-366

Over the past decades, obesity has become an epidemic worldwide. Obesity impacts health burdens heterogeneously by the regional distribution of fat, not total body fat quantity. Epidemiologic studies reported that regional body fat distribution could represent a significant risk factor for insulin resistance (1), type 2 diabetes mellitus, and cardiovascular disease (2). Nonalcoholic fatty liver disease (NAFLD) affects approximately a fourth of the population worldwide and has been linked with overweight/obesity. However, NAFLD can be seen in individuals without overweight/obesity, which is called lean NAFLD. It has been shown that in terms of body fat distribution, visceral adipose tissue (VAT) has a stronger association with NAFLD and severity in NAFLD than subcutaneous adipose tissue (SAT) (3-6). Total body fat quantity, as assessed by body mass index (BMI), does not reflect regional body fat distribution (7). Although waist circumference is a relatively accurate measurement to assess abdominal obesity, it does not represent body fat distribution because it is unable to distinguish VAT from SAT (8,9). A study demonstrated a strong correlation between sagittal abdominal diameter and VAT, whereas waist circumference was correlated with SAT more than VAT (10). Thus, BMI and waist circumference may be imperfect measurements to determine body fat distribution and risk stratification for individuals with NAFLD.

We summarized studies that investigated the association between body fat distribution and NAFLD and the severity of NAFLD in *Table 1* (3-5,11-14). A Korean study revealed that VAT area is the independent risk factor for elevated alanine aminotransferase (ALT) among individuals with NAFLD in both men [odds ratio (OR) =2.36; 95% confidence interval (CI): 1.48–3.76 comparing higher VAT quartile *vs.* lower VAT quantile; P for trend <0.001] and women (OR =3.70; 95% CI: 1.52–8.99; P for trend <0.001) independent of BMI and SAT area (5). In terms of the severity of NAFLD, a pilot study showed that VAT area might be dose-dependently linked with liver inflammation and fibrosis independent of insulin resistance (11). A subsequent study based on 456 histology-confirmed NAFLD and control demonstrated that VAT area was independently associated with nonalcoholic steatohepatitis (NASH) (OR =1.17; 95% CI: 1.05–1.32 per 10 cm^2 increase of VAT area) and significant fibrosis (F2–F4) (OR =1.21; 95% CI: 1.07–1.37 per 10 cm^2 increase of VAT area) (4). The earlier studies were mainly cross-sectional and could not draw the causal relationship between VAT and NAFLD. A cohort study (n=2,017) investigated the longitudinal association between body fat distribution and NAFLD incidence/regression (3). During the median follow-up of 4.4 years, a higher VAT area at baseline was longitudinally associated with a higher incidence of NAFLD in a dose-dependent

^ ORCID: Karn Wijarnpreecha, 0000-0002-6232-6343; Aijaz Ahmed, 0000-0002-3609-8586; Donghee Kim, 0000-0003-1919-6800.

Table 1 Summary of studies regarding the association between body fat distribution and NAFLD and severity of NAFLD

Study	Country	Study design	Number of participants	Participants	Mean age of participants (years)	Percentage of women	Body fat distribution	Body fat ascertainment	Definition of NAFLD	Outcomes (OR or HR)		Confounder adjustment
Van der Poorten *et al.* 2008, (11)	Australia	Cross-sectional study	38	Adults with biopsy-proven NAFLD from a tertiary liver clinic	51±12	42	VAT; SAT; VAT/SAT ratio	Magnetic resonance examination	Biopsy-proven NAFLD with alcohol intake less than 40 g per week	Each 1% increase in visceral fat increases OR of liver inflammation OR 2.4 (95% CI: 1.3–4.2) and liver fibrosis OR 3.5 (95% CI: 1.7–7.1)	VAT is an independent predictor of NASH OR 2.1 (95% CI: 1.1–4.2) and liver fibrosis OR 2.9 (95% CI: 1.4–6.3)	HOMA-IR and liver fat
Ruhl *et al.* 2010, (12)	United States	Cross-sectional study	11,821	US adults without hepatitis B or C infection, non-pregnant, from the NHANES database between 1999–2004	N/A	50	VAT or trunk fat	DEXA	Not study for NAFLD. Assess the increased of ALT level	Men: elevated ALT in the highest quintile of trunk fat OR 13.8 (95% CI: 5.4–35.3)	Women: elevated ALT in the highest quintile of trunk fat OR 7.8 (95% CI: 3.9–15.8)	Age, sex, ethnicity, cigarette smoking, alcohol consumption, glucose status, total cholesterol
Chung *et al.* 2015, (5)	South Korea	Cross-sectional study	3,712	Adults without hepatitis B or C infection with no significant alcohol consumption or other liver diseases who underwent routine health checkups	52±10	44.5	VAT; SAT	Computed tomography scan	Ultrasound demonstrated hepatic steatosis with no other causes of liver disease	Men NAFLD: elevated ALT in the highest quintile of VAT OR 2.8 (95% CI: 1.8–4.4)	Women NAFLD: elevated ALT in the highest quintile of VAT OR 4.4 (95% CI: 1.9–10.2)	Age, smoking, systolic blood pressure, fasting glucose, triglyceride, HDL, menopause (women only), hormone replacement therapy (women only)
Yu *et al.* 2015, (4)	South Korea	Cross-sectional study	456 (324 NAFLD and 132 controls)	Adults with clinically suspected NAFLD who underwent liver biopsy at two tertiary hospitals between July 2000 and August 2014	35±14	34.4	VAT; SAT	Computed tomography scan	Biopsy-proven NAFLD without other causes of liver disease	VAT area associated with NAFLD with significant fibrosis (F2–F4) OR 1.2 (95% CI: 1.1–1.4) per 10 cm^2 increase of VAT area	VAT area associated with NASH in NAFLD OR 1.2 (95% CI: 1.1–1.3) per 10 cm^2 increase of VAT area	Age, sex, body mass index, platelet count, smoking, hypertension, diabetes, SAT
Kim *et al.* 2016, (3)	South Korea	Retrospective cohort study	2,017	Adults without hepatitis B or C infection with no significant alcohol consumption or other liver diseases from 2007–2008 whom follow-up health screening between 2011–2013 with median follow-up time: 4.43 years	No incident NAFLD: 51±9 Incident NAFLD: 52±9	No incident NAFLD: 53.0 Incident NAFLD: 31.2	VAT; SAT	Computed tomography scan	Ultrasound demonstrated hepatic steatosis with no other causes of liver disease	VAT is associated with a higher incidence of NAFLD with HR 2.2 (95% CI: 1.3–3.9)	SAT is associated with regression of NAFLD with HR 2.3 (95% CI: 1.3–4.1)	Age, sex, body mass index, smoking status, diabetes, hypertension, soft drink, physical activity, VAT area, SAT area, total cholesterol, triglyceride, HDL
Kim *et al.* 2018, (13)	South Korea	Retrospective cohort study	956	Adults with abdominal fat data, without hepatitis B or C infection with no significant alcohol consumption or other liver diseases from 2007–2008 who follow-up health screening between 2011–2013	No incident NAFLD: 52±9 Incident NAFLD: 52±8	No incident NAFLD: 49.9 Incident NAFLD: 29.7	VAT; SAT	Computed tomography scan	Ultrasound demonstrated hepatic steatosis with no other causes of liver disease	Increasing VAT during follow-up is associated with a higher incidence of NAFLD with HR 2.5 (95% CI: 1.6–3.9)	Increasing VAT during follow-up is inversely associated with the regression of NAFLD with HR 0.4 (95% CI: 0.2–0.8)	Age, sex, body mass index, diabetes, difference of VAT area, difference of SAT area, VAT area SAT area at baseline
Ciardullo *et al.* 2022, (14)	United States	Cross-sectional study	2,228	Adults aged 18–59 years without known liver conditions or significant alcohol consumption from the NHANES database between 2017–2018	Male: CAP ≥274: 41±1; CAP <274: 35±1 Female: CAP ≥274: 42±1; CAP <274: 37±1	49.9	Android/gynoid ratio	DEXA	Transient elastography showed ≥274 dB/m for NAFLD diagnosis and median liver stiffness measurement ≥8.0 kPa for significant liver fibrosis (F2–F4)	Relationship between A/G ratio and NAFLD: Men, OR 1.8 (95% CI: 1.1–3.0); women, OR 1.9 (95% CI: 1.1–3.4)	Relationship between A/G ratio and liver fibrosis: men: OR 0.6 (95% CI: 0.3–1.1); women: OR 2.1 (95% CI: 1.1–4.0)	Age, race, Hispanic origin, diabetes, cigarette smoking, body mass index

NAFLD, nonalcoholic fatty liver disease; OR, odds ratio; HR, hazard ratio; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; CI, confidence interval; HOMA-IR, homeostasis model assessment of insulin resistance; NHANES, National Health and Nutrition Examination Survey; N/A, not applicable; DEXA, dual-energy x-ray absorptiometry; ALT, alanine aminotransferase; HDL, high-density lipoprotein; NASH, nonalcoholic steatohepatitis; CAP, controlled attenuation parameter; A/G ratio, android/gynoid ratio.

manner [hazard ratio (HR) =2.23; 95% CI: 1.28–3.89 for the highest quintile *vs.* lowest quintile of VAT, P for trend =0.002] after adjustment for age, sex, BMI, smoking status, diabetes, hypertension, soft drink consumption, physical activity, and lipid profiles, and SAT area. In contrast, an increased SAT area at baseline was significantly associated with regression of NAFLD (HR =2.30; 95% CI: 1.28–4.12 for the highest quintile *vs.* lowest quintile of SAT, P for trend =0.002). This study suggests that a specific type of body fat, such as VAT, is the risk factor for NAFLD, while SAT might be a possible metabolic sink for NAFLD. The following study reported that incremental accumulation of VAT area over 5 years is associated with the incident NAFLD, independent of VAT and SAT area at baseline (13). In contrast, incremental change in VAT area during follow-up is inversely associated with regressed NAFLD (13). In this study, the authors found no significant interaction between gender and change in VAT and SAT area during the follow-up for incidence of NAFLD. In addition, all the above studies used sex-specific quartile or quintile for VAT and SAT areas and adjusted for sex because body fat distribution was different between men and women. Accumulating current works of literature, we can suggest that visceral obesity, not general obesity, is most likely the crucial target for interventions in the treatment of NAFLD.

A US population-based study using the National Health and Nutrition Examination Survey (NHANES) 1999–2004 reported the relationship between liver injury and body composition by dual X-ray absorptiometry (DXA) (12). They showed a strong association of higher trunk fat with abnormal ALT among men and women, independent of BMI, extremity fat, trunk or extremity lean mass, waist circumference, and other liver injury risk factors. The article published by Ciardullo *et al.* (14) investigated the association between body fat distribution by DXA and NAFLD and significant fibrosis in the contemporary US population. This cross-sectional study used the NHANES 2017–2018 dataset, which had a unique opportunity to use transient elastography to define NAFLD and significant fibrosis. The authors assessed body fat distribution as an android/gynoid ratio (A/G ratio). In general, the gynoid fat distribution pattern (pear-shaped), which may be characterized by high SAT accumulation in the thigh and hip areas, may be associated with a lower risk of cardiometabolic abnormalities compared with the android fat distribution pattern (apple-shaped), characterized by increased VAT in the abdominal area (14). Among 1,115 males and 1,113 females, weighted prevalence of NAFLD was 41.5% and 29.9%, with significant fibrosis (≥ F2) of 7.0% and 4.0%, respectively (14). Multivariable logistic analysis adjusted for age, race/ethnicity, diabetes, smoking, and BMI, a higher A/G ratio was associated with an increased prevalence of NAFLD in both males [OR =1.79; 95% CI: 1.07–2.99 per 1-standard deviation (SD) increase; P=0.029] and females (OR =1.95; 95% CI: 1.11–3.41; P=0.023) (14). In terms of fibrosis, the A/G ratio was associated with significant fibrosis in females (OR =2.09; 95% CI: 1.11–3.97; P=0.026). In contrast, the A/G ratio was inversely associated with significant fibrosis in males (OR =0.56; 95% CI: 0.29–1.08), although the association was marginal and statistically insignificant (P=0.078). Interestingly, general obesity defined by BMI remained an independent risk factor for NAFLD and significant fibrosis in both males and females. The finding supported that the higher A/G ratio, which the android fat distribution pattern may characterize, may be considered the surrogate marker for NAFLD. A recent meta-analysis showed that females are at higher risk of developing liver fibrosis progression than males once NAFLD has developed (15). The association between the A/G ratio and significant fibrosis in females, not males, may be partly explained (14). However, the exact mechanism to explain the discrepancy is not fully understood, and further studies are needed to elaborate on this finding.

This study was based on a representative sample of US adults (aged 18–59 years), which can be generalized to the current US multiethnic population. Compared to the previous study based on the NHANES 1999–2004, this study used transient elastography to define NAFLD and significant fibrosis, not elevated ALT. Although this cross-sectional study (14) gives valuable information, some limitations need to be considered. First, the A/G ratio may assume body fat distribution but could not accurately distinguish between VAT and SAT. Second, although the authors adjusted for age, race/ethnicity, diabetes, smoking, and BMI in the multivariable model, there are still multiple confounders such as demographic, lifestyle (diet and exercise), hormone replacement therapy, and metabolic risk factors to investigate the independent association between the A/G ratio and NAFLD/significant fibrosis. Third, it is more clinically relevant to use the A/G ratio as a continuous variable, not a 1-SD increase, to investigate whether the A/G ratio can be a clinical surrogate marker for NAFLD and significant fibrosis in clinical practice. Further longitudinal studies are warranted to assess the causal relationship between fat distribution and NAFLD and liver fibrosis among the US population. Moreover, future longitudinal

studies that elaborate on the mechanism behind the different effects of fat distribution and NAFLD, significant fibrosis among males and females are warranted.

In summary, the literature on the effect of body fat distribution on NAFLD or NAFLD-related liver fibrosis is growing and accumulating. The article by Ciardullo *et al.* (14) sheds light on the puzzle for the sex-related association between body fat distribution and NAFLD/significant fibrosis by transient elastography in the current general US population. Since there is still no approved medication for NASH or NAFLD, lifestyle modification and therapeutic intervention to decrease VAT or intervene in body fat distribution may help prevent the development and slow the progression of NAFLD or NAFLD-related liver fibrosis.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Hepatobiliary Surgery and Nutrition*. The article did not undergo external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-22-366/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Lee SM, Ryu KJ, Son S, et al. Body fat distribution and insulin resistance among Korean middle-aged women: a Korean National Health and Nutrition Examination Survey. Obstet Gynecol Sci 2022;65:468-76.
2. Klarqvist MDR, Agrawal S, Diamant N, et al. Silhouette images enable estimation of body fat distribution and associated cardiometabolic risk. NPJ Digit Med 2022;5:105.
3. Kim D, Chung GE, Kwak MS, et al. Body Fat Distribution and Risk of Incident and Regressed Nonalcoholic Fatty Liver Disease. Clin Gastroenterol Hepatol 2016;14:132-8.e4.
4. Yu SJ, Kim W, Kim D, et al. Visceral Obesity Predicts Significant Fibrosis in Patients With Nonalcoholic Fatty Liver Disease. Medicine (Baltimore) 2015;94:e2159.
5. Chung GE, Kim D, Kwark MS, et al. Visceral adipose tissue area as an independent risk factor for elevated liver enzyme in nonalcoholic fatty liver disease. Medicine (Baltimore) 2015;94:e573.
6. Saponaro C, Sabatini S, Gaggini M, et al. Adipose tissue dysfunction and visceral fat are associated with hepatic insulin resistance and severity of NASH even in lean individuals. Liver Int 2022;42:2418-27.
7. Prentice AM, Jebb SA. Beyond body mass index. Obes Rev 2001;2:141-7.
8. Kuk JL, Lee S, Heymsfield SB, et al. Waist circumference and abdominal adipose tissue distribution: influence of age and sex. Am J Clin Nutr 2005;81:1330-4.
9. Pou KM, Massaro JM, Hoffmann U, et al. Patterns of abdominal fat distribution: the Framingham Heart Study. Diabetes Care 2009;32:481-5.
10. Yim JY, Kim D, Lim SH, et al. Sagittal abdominal diameter is a strong anthropometric measure of visceral adipose tissue in the Asian general population. Diabetes Care 2010;33:2665-70.
11. van der Poorten D, Milner KL, Hui J, et al. Visceral fat: a key mediator of steatohepatitis in metabolic liver disease. Hepatology 2008;48:449-57.
12. Ruhl CE, Everhart JE. Trunk fat is associated with increased serum levels of alanine aminotransferase in the United States. Gastroenterology 2010;138:1346-56, 1356.e1-3.
13. Kim D, Chung GE, Kwak MS, et al. Effect of longitudinal changes of body fat on the incidence and regression of nonalcoholic fatty liver disease. Dig Liver Dis 2018;50:389-95.
14. Ciardullo S, Oltolini A, Cannistraci R, et al. Sex-related association of nonalcoholic fatty liver disease and liver fibrosis with body fat distribution in the general US

population. Am J Clin Nutr 2022;115:1528-34.
15. Balakrishnan M, Patel P, Dunn-Valadez S, et al. Women Have a Lower Risk of Nonalcoholic Fatty Liver Disease but a Higher Risk of Progression vs Men: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol 2021;19:61-71.e15.

Cite this article as: Wijarnpreecha K, Ahmed A, Kim D. Body fat distribution: a crucial target for intervention in nonalcoholic fatty liver disease and fibrosis. HepatoBiliary Surg Nutr 2022;11(5):738-742. doi: 10.21037/hbsn-22-366