

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Association between serum triglyceride to high-density lipoprotein cholesterol ratio and sarcopenia among elderly patients with diabetes: A secondary data analysis of the China Health and Retirement Longitudinal Study
<b>AUTHORS</b>	Lin, Yinghe; Zhong, Shanshan; Sun, Zhihua

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Aktas, Gulali Bolu Abant İzzet Baysal University
<b>REVIEW RETURNED</b>	28-May-2023

<b>GENERAL COMMENTS</b>	<p>Association between serum triglyceride to high-density lipoprotein cholesterol ratio and sarcopenia among elderly patients with diabetes: Findings from the China Health and Retirement Longitudinal Study titled study is carefully read and reviewed. Authors studied the association between triglyceride to HDL cholesterol ratio and sarcopenia in diabetic patients. Although the paper sounds scientific enough there are several issues that require revision.</p> <ul style="list-style-type: none"><li>- Introduction fails to provide adequate background to express the study rationale. Why authors studied serum triglyceride to HDL cholesterol ratio in sarcopenic diabetic subjects. HDL cholesterol based markers are attracted great attention in recent years and they have been related with various inflamamtory and metabolic conditions such as hypertension (Postgraduate Medicine 2022;134(3): 297-302. DOI: 10.1080/00325481.2022.2039007), non-alcoholic liver steatosis (Rev Assoc Med Bras 2021;67(4):549-554. DOI: 10.1590/1806-9282.20201005.), thyroiditis (Rom. J. Intern. Med. 2021;59(4):403-408. DOI: 10.2478/rjim-2021-0023.), metabolic syndrome (Rev Assoc Med Bras 2019; 65(1):9-15. DOI: 10.1590/1806-9282.65.1.9) type 2 Diabetes Mellitus (Aging Male. 2020;23(5):1098-1102. DOI: 10.1080/13685538.2019.1678126), and diabetic kidney injury (Postgraduate Medicine, 2023. DOI: 10.1080/00325481.2023.2214058). On the other hand, sarcopenia (Acta Endocrinologica (Buc), 2020;16(2):263-266. doi: 10.4183/aeb.2020.263) and related disorder; frailty (Bratisl Med J 2021;122(2):116–119. DOI: 10.4149/BLL_2021_017) are associated with increased burden of inflammation. Authors should improve the background accordingly.</li><li>- Expression of the methodology is very well and statistics are corerct. Yet, authors didnt stated the normality analysis that applied to the study parameters (variables). Please mention appropriately.</li><li>- Presentation of the results is adequate. Discussion is fair but could be better than its current form. Comparison of other studies</li></ul>
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	<p>that found triglyceride to HDL cholesterol ratio as a marker of metabolic conditions along with the results of the present study is advised. For example, higher levels of triglyceride to HDL cholesterol ratio have been reported in type 2 Diabetes mellitus (<i>Acta facultatis medicae Naissensis</i> 2022; 39(1):66-73. DOI: 10.5937/afmnai39-33239), in hepatosteatois (<i>Experimental Biomedical Research</i>, 2021, 4.3: 224-229), and in hypertension (<i>Precision Medical Sciences</i> 2022;11(3):100–105. DOI: 10.1002/prm2.12080). Moreover, authors are recommended to comment on the clinical translation of the findings in present study.</p> <ul style="list-style-type: none"> <li>- Five of the references are too old and if they are not crucial should be removed or replaced with new literature.</li> <li>- Bold expression of the significant p values in the tables would make following ease.</li> </ul>
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<b>REVIEWER</b>	Familoni, Oluranti Olabisi Onabanjo University Teaching Hospital, medicine
<b>REVIEW RETURNED</b>	17-Jun-2023

<b>GENERAL COMMENTS</b>	<p>An otherwise useful manuscript that however requires some minor revision</p> <p>The Results should start with a Table showing ALL the study participants before breaking into genders.</p> <p>The Discussion is not robust enough! For example the authors need to let us know why there results is different from the Korean study despite being in the same area and showing similar demographics</p> <p>The roles of Sarcopaenia obesity, fat infiltration, ectopic fat deposition and adipokines in influencing the results of dyslipidaemia in this study will not be out of place, Why did TG/HDL-C correlate with muscle mass and not strength?</p>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Gulali Aktas, Bolu Abant İzzet Baysal University

Comments to the Author:

Association between serum triglyceride to high-density lipoprotein cholesterol ratio and sarcopenia among elderly patients with diabetes: Findings from the China Health and Retirement Longitudinal Study titled study is carefully read and reviewed. Authors studied the association between triglyceride to HDL cholesterol ratio and sarcopenia in diabetic patients. Although the paper sounds scientific enough there are several issues that require revision.

- Introduction fails to provide adequate background to express the study rationale. Why authors studied serum triglyceride to HDL cholesterol ratio in sarcopenic diabetic subjects. HDL cholesterol based markers are attracted great attention in recent years and they have been related with various inflamamtory and metabolic conditions such as hypertension (*Postgraduate Medicine* 2022;134(3): 297-302. DOI: 10.1080/00325481.2022.2039007), non-alcoholic liver steatosis (*Rev Assoc Med Bras* 2021;67(4):549-554. DOI: 10.1590/1806-9282.20201005.), thyroiditis (*Rom. J. Intern. Med.* 2021;59(4):403-408. DOI: 10.2478/rjim-2021-0023.), metabolic syndrome (*Rev Assoc Med Bras* 2019; 65(1):9-15. DOI: 10.1590/1806-9282.65.1.9) type 2 Diabetes Mellitus (*Aging Male*. 2020;23(5):1098-1102. DOI: 10.1080/13685538.2019.1678126), and diabetic kidney injury (*Postgraduate Medicine*, 2023. DOI: 10.1080/00325481.2023.2214058). On the other hand, sarcopenia (*Acta Endocrinologica (Buc)*, 2020;16(2):263-266. doi: 10.4183/aeb.2020.263) and related

disorder; frailty (Bratisl Med J 2021;122(2):116–119. DOI: 10.4149/BLL\_2021\_017) are associated with increased burden of inflammation. Authors should improve the background accordingly.

Thank you very much for the reviewer's valuable comments.

According to the comments, we reviewed all the recommended studies. Meanwhile, we searched the relevant studies again and tried to improve the background of this study. It emphasized the academic attention to high-density lipoprotein cholesterol (HDL-C) based markers and the more likely potential relationship between the markers, diabetes, and sarcopenia. At the same time, the references have been updated appropriately.

Unfortunately, due to the limitation of the number of references and the need of the study subject, the author conducted an in-depth discussion and quoted the more essential and appropriate studies of the recommended literature by the reviewer [1-4] instead of quoting them one by one.

However, it does not mean the authors ignored the reviewer's comments.

Thanks again to the reviewer for the valuable comments on the crucial improvement of our study.

#### References

[1] Kosekli MA, Kurtkulagii O, Kahveci G, et al. The association between serum uric acid to high density lipoprotein-cholesterol ratio and non-alcoholic fatty liver disease: the abund study. *Rev Assoc Med Bras* (1992). 2021;67(4):549-554. doi: 10.1590/1806-9282.20201005.

[2] Kurtkulagi O, Tel BMA, Kahveci G, et al. Hashimoto's thyroiditis is associated with elevated serum uric acid to high density lipoprotein-cholesterol ratio. *Rom J Intern Med*. 2021;59(4):403-408. doi: 10.2478/rjim-2021-0023.

[3] Aktas G, Kocak MZ, Bilgin S, et al. Uric acid to HDL cholesterol ratio is a strong predictor of diabetic control in men with type 2 diabetes mellitus. *Aging Male*. 2020;23(5):1098-1102. doi: 10.1080/13685538.2019.1678126.

[4] Aktas G, Yilmaz S, Kantarci DB, et al. Is serum uric acid-to-HDL cholesterol ratio elevation associated with diabetic kidney injury? *Postgrad Med*. 2023;135(5):519-523. doi: 10.1080/00325481.2023.2214058.

- Expression of the methodology is very well and statistics are correct. Yet, authors did not state the normality analysis that applied to the study parameters (variables). Please mention appropriately. According to the comment, we have revised the statistical method of this study in more detail and pointed out that the Kolmogorov-Smirnov test was performed in this study to test the normality of the continuous variables.

- Presentation of the results is adequate. Discussion is fair but could be better than its current form. Comparison of other studies that found triglyceride to HDL cholesterol ratio as a marker of metabolic conditions along with the results of the present study is advised. For example, higher levels of triglyceride to HDL cholesterol ratio have been reported in type 2 Diabetes mellitus (*Acta facultatis medicae Naissensis* 2022; 39(1):66-73. DOI: 10.5937/afmna139-33239), in hepatosteatosis (*Experimental Biomedical Research*, 2021, 4.3: 224-229), and in hypertension (*Precision Medical Sciences* 2022;11(3):100–105. DOI: 10.1002/prm2.12080). Moreover, authors are recommended to comment on the clinical translation of the findings in present study.

Thanks again to the reviewer for the significant comments.

Based on the comments, we reviewed all the recommended studies and searched the relevant studies again to enrich the discussion in this study. It is revised in the article that the triglyceride to high-density lipoprotein cholesterol ratio (TG/HDL-C ratio) as a marker of metabolic conditions has been presented in recent studies. At the same time, the authors proposed the clinical translation of our findings that as an easily accessible parameter, TG/HDL-C ratio may help in screening sarcopenia in elderly diabetic patients, which may facilitate the prevention and treatment of sarcopenia in people with diabetes. Similarly, the references have been updated appropriately.

It is also sorry that due to the limitation of the number of references and the need of the study subject, we quoted the more critical and appropriate studies of the recommended literature by the reviewer [1] instead of quoting them one by one.

However, it does not mean that the authors also ignored the reviewer's comments.

Thanks again for the meaningful comments on the crucial improvement of our study.

#### References

[1] Bilgin S, Aktas G, Tel BMA, et al. Triglyceride to High Density Lipoprotein Cholesterol Ratio is Elevated in Patients with Complicated Type 2 Diabetes Mellitus. *Acta facultatis medicae Naissensis*. 2022;39(1):66-73. DOI: 10.5937/afmna39-33239.

- Five of the references are too old and if they are not crucial should be removed or replaced with new literature.

According to the review of the original citations, the following five literatures were found to be the earliest published:

[Original reference 9] Sayer AA. Sarcopenia. *BMJ*. 2010;10:341.c4097. doi: 10.1136/bmj.c4097.

[Original reference 18] Cordero A, Andrés E, Ordoñez B, León M, Laclaustra M, Grima A, et al. Usefulness of triglycerides-to-high-density lipoprotein cholesterol ratio for predicting the first coronary event in men. *Am J Cardiol*. 2009;104(10):393-397. doi: 10.1016/j.amjcard.2009.07.008.

[Original reference 19] Cordero A, Andrés E, Ordoñez B, León M, Laclaustra M, Grima A, et al. Usefulness of triglycerides-to-high-density lipoprotein cholesterol ratio for predicting the first coronary event in men. *Am J Cardiol*. 2009;104(10):393-397. doi: 10.1016/j.amjcard.2009.07.008.

[Original reference 24] Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009; 150(9):604-612. doi: 10.7326/0003-4819-150-9-200905050-00006.

[Original reference 25] Wen X, Wang M, Jiang CM, Zhang YM. Anthropometric equation for estimation of appendicular skeletal muscle mass in Chinese adults. *Asia Pac J Clin Nutr*. 2011; 20(4):551-556.

According to the comment, firstly, the original reference 9, 18, and 19 have been deleted or replaced. Secondly, the original reference 24 provided a practical and widely cited formula for calculating estimated glomerular filtration rate (eGFR). This study also used the literature formula to calculate eGFR, so it was retained. Thirdly, the original reference 25 provided a formula for estimating Chinese adults' appendicular muscle mass (ASM). Our study used the valid formula for calculating ASM, so it was reserved.

- Bold expression of the significant p values in the tables would make following ease.

Based on the comment, the format has been revised and the significant p values have been highlighted in the table by bold font.

Reviewer: 2

Dr. Oluranti Familoni, Olabisi Onabanjo University Teaching Hospital

Comments to the Author:

An otherwise useful manuscript that however requires some minor revision

- The Results should start with a Table showing ALL the study participants before breaking into genders.

Based on the comment, we have revised the results section and presented baseline of total participants at first in this study, followed by gender stratification analysis.

- The Discussion is not robust enough!

Thank you very much for the reviewer's significant comments. We further refined the discussion section based on the reviewer's comments in this study.

- For example the authors need to let us know why there results is different from the Korean study despite being in the same area and showing similar demographics

In fact, our finding was contrary to the Korean study [1] and the reason for the conflicting results is unclear. Previous studies have shown that study design, gene diversity, lifestyle factors and disease advancement in different populations may lead to variations in lipid profiles [2,3]. First, this study followed AWGS 2019 for the evaluation of sarcopenia [4], while the Korean study was published before the consensus [1], which may have lead to selection bias. Second, gene polymorphisms affecting the lipid profiles in the Chinese and Koreans remains undefined but cannot be ignored, because a study reported significant difference in lipid profiles between the Chinese and Korean adolescents populations [5]. Third, unlike the Korean study [1], this study was confined to elderly Chinese patients with diabetes, and the lipid profiles of diabetes patients differ from those of the general population [6], which may also be one of the reasons for the inconsistent results.

#### References

- [1] Chung TH, Kwon YJ, Shim JY, et al. Association between serum triglyceride to high-density lipoprotein cholesterol ratio and sarcopenia in elderly Korean males: The Korean National Health and Nutrition Examination Survey. *Clin Chim Acta*. 2016; 463:165-168. doi: 10.1016/j.cca.2016.10.032.
- [2] Wang N, Chen M, Fang D. Relationship between serum triglyceride to high-density lipoprotein cholesterol ratio and sarcopenia occurrence rate in community-dwelling Chinese adults. *Lipids Health Dis*. 2020;19(1):248. doi: 10.1186/s12944-020-01422-4.
- [3] Fu Q, Zhang Z, Hu W, et al. The correlation of triglyceride/high-density lipoprotein cholesterol ratio with muscle mass in type 2 diabetes patients. *BMC Endocr Disord*. 2023;23(1):93. doi: 10.1186/s12902-023-01349-8.
- [4] Chen LK, Woo J, Assantachai P, et al. Asian Working Group for Sarcopenia: 2019 Consensus Update on Sarcopenia Diagnosis and Treatment. *J Am Med Dir Assoc*. 2020;21(3):300–307.e2. doi: 10.1016/j.jamda.2019.12.012.
- [5] Kim MK, Kwak I, Ki M, et al. Comparison of serum lipid levels among Korean, Korean-Chinese, and Han-Chinese adolescents. *J Adolesc Health*. 2005;36(6):501-507. doi: 10.1016/j.jadohealth.2005.01.014.
- [6] American Diabetes Association. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2020. *Diabetes Care*. 2020;43(Suppl 1):S14-S31. doi: 10.2337/dc20-S002.

- The roles of Sarcopaenia obesity, fat infiltration, ectopic fat deposition and adipokines in influencing the results of dyslipidaemia in this study will not be out of place,

Indeed, the above comment cannot be ignored. Therefore, we included body mass index (BMI) for statistical correction. At the same time, the potential influence by obesity, fat infiltration, ectopic fat deposition and adipokines between sarcopaenia insulin resistance and dyslipidaemia was supplemented in the discussion section.

- Why did TG/HDL-C correlate with muscle mass and not strength?

In this study, we observed that the significant association between TG/HDL-C ratio and muscle mass in male and female elderly diabetics were consistent, while the significant association between TG/HDL-C ratio and muscle strength were found only among female elderly diabetics. Therefore, we don't know if I can interpret the question as why was TG/HDL-C more closely related to muscle mass than muscle strength?

Compared with muscle strength and function, this closer relationship between TG/HDL-C ratio and muscle mass was supported by previous studies and attributed to their potential interactions [1-3]. As a marker associated with insulin resistance, TG/HDL-C ratio may reflect the vicious cycle between sarcopenia and insulin resistance [3]. Sarcopenia is mainly characterized by a decrease in muscle mass along with an increase in intramuscular fat. Since skeletal muscle plays an important role in insulin-mediated glucose disposal, lower skeletal muscle mass is likely to diminish this effect. Moreover, inappropriate secretion of adipokines by intramuscular fat may potentially lead to increased

insulin resistance and sarcopenia. Muscle protein metabolism is influenced by insulin resistance, which promotes muscle sarcopenia resulting in loss of skeletal muscle mass.

References

[1] Chung TH, Kwon YJ, Shim JY, et al. Association between serum triglyceride to high-density lipoprotein cholesterol ratio and sarcopenia in elderly Korean males: The Korean National Health and Nutrition Examination Survey. Clin Chim Acta. 2016; 463:165-168. doi: 10.1016/j.cca.2016.10.032.  
 [2] Wang N, Chen M, Fang D. Relationship between serum triglyceride to high-density lipoprotein cholesterol ratio and sarcopenia occurrence rate in community-dwelling Chinese adults. Lipids Health Dis. 2020;19(1):248. doi: 10.1186/s12944-020-01422-4.  
 [3] Fu Q, Zhang Z, Hu W, et al. The correlation of triglyceride/high-density lipoprotein cholesterol ratio with muscle mass in type 2 diabetes patients. BMC Endocr Disord. 2023;23(1):93. doi: 10.1186/s12902-023-01349-8.

**VERSION 2 – REVIEW**

<b>REVIEWER</b>	Aktas, Gulali Bolu Abant İzzet Baysal University
<b>REVIEW RETURNED</b>	17-Jul-2023

<b>GENERAL COMMENTS</b>	The revisions done in the text are satisfactory. There is nothing more that require further revision. I recommend publication of the manuscript in its current form.
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<b>REVIEWER</b>	Familoni, Oluranti Olabisi Onabanjo University Teaching Hospital, medicine
<b>REVIEW RETURNED</b>	22-Jul-2023

<b>GENERAL COMMENTS</b>	Authors seem to have addressed the issues i raised, though i would have prefereed for the issues raised to be highlighted and specific answers made bold
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