

## **Circulating plasma microRNA-126, -145 and -155 and their association with atherosclerotic plaque characteristics**

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Handling editor:

Michal Heger

*Department of Pharmaceutics, Utrecht University, the Netherlands*

*Photonanomedicine, Jiaxing University Medical College, Zhejiang, China*

Review timeline:

Received: 20 October, 2019  
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1<sup>st</sup> Editorial decision

25-Nov-2019

Ref.: Ms. No. JCTRes-D-19-00023

Circulating plasma microRNA-126, -145 and -155 and their association with atherosclerotic plaque characteristics.

Journal of Clinical and Translational Research

Dear author(s),

Reviewers have submitted their critical appraisal of your paper. The reviewers' comments are appended below. Based on their comments and evaluation by the editorial board, your work was FOUND SUITABLE FOR PUBLICATION AFTER MINOR REVISION.

If you decide to revise the work, please itemize the reviewers' comments and provide a point-by-point response to every comment. An exemplary rebuttal letter can be found on at <http://www.jctres.com/en/author-guidelines/> under "Manuscript preparation." Also, please use the track changes function in the original document so that the reviewers can easily verify your responses.

Your revision is due by Dec 25, 2019.

To submit a revision, go to <https://www.editorialmanager.com/jctres/> and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely,

Michal Heger  
Editor-in-Chief  
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: The authors examined the association between mirRNAs 126, 145 and 155 and atherosclerotic plaque intravascular ultrasound characteristics. They show that mirRNAs 126, 145 and 155 are associated with plaque necrolipidic content. The strength of this study is that it includes IVUS characteristics of patient with CAD. Major limitations are sample size and lack of characterization of miR source, kinetics and function.

1. Is it possible to provide a Figure to aid with Table 2 to demonstrate how fibrotic, necrotic, lipidic, and calcific lesions were quantified?
2. Can you clarify what necrolipidic means, is that a combination of lipiditic and necrotic?
3. Please highlight the clinical correlate/implications of necrolipidic lesions.
4. Is it possible to enroll more patients to increase N?
5. Will you provide q-PCR data, raw value?
6. Please comment on the strength of the association of miR base on analysis
7. Please comment on potential use of mirRNAs 126, 145 and 155 as plasma biomarker if the result are divergent from previous studies supporting them as artheroprotective.

Thank you for your work.

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Author's response

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[evija.knoka@gmail.com](mailto:evija.knoka@gmail.com)

Riga, 11 December 2019

Re: revision No. JCTRes-D-19-00023

Dear Michal Heger,

Thank you for finding our paper "Circulating plasma microRNA-126, -145 and -155 and their association with atherosclerotic plaque characteristics." suitable for publication. We are grateful for the reviewers comments and have addressed all comments using the track changes function in Word

(attached as supplementary material not for publication). Moreover, every modification or rebuttal of the reviewer's comments is detailed per comment below in red italics. On behalf of the authors, kindest regards,  
Evija Knoka

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#### REVIEWER COMMENTS

Reviewer #1: The authors examined the association between mirRNAs 126, 145 and 155 and atherosclerotic plaque intravascular ultrasound characteristics. They show that mirRNAs 126, 145

and 155 are associated with plaque necrolipidic content. The strength of this study is that it includes

IVUS characteristics of patient with CAD. Major limitations are sample size and lack of characterization of miR source, kinetics and function.

1. Is it possible to provide a Figure to aid with Table 2 to demonstrate how fibrotic, necrotic, lipidic, and calcific lesions were quantified?

*The comment has been addressed as Figure 2.*

2. Can you clarify what necrolipidic means, is that a combination of lipidic and necrotic?  
*The*

*comment has been addressed in the text patients and methods section.*

*“Increased size of lipid-rich necrotic plaque tissue is believed to be a risk factor for atherosclerotic plaque rupture, therefore a combination of lipidic and necrotic tissue was determined and defined as necrolipidic tissue and used in further analysis”.*

3. Please highlight the clinical correlate/implications of necrolipidic lesions.

*The comment has been addressed in the text patients and methods section.*

*“Increased size of lipid-rich necrotic plaque tissue is believed to be a risk factor for atherosclerotic plaque rupture, therefore a combination of lipidic and necrotic tissue was determined and defined as necrolipidic tissue and used in further analysis”.*

4. Is it possible to enroll more patients to increase N?

*We are aware that the small sample size is a limitation to our study, however, considering the costs*

*for microRNA expression determination in our country, we are currently unable to enroll more patients.*

5. Will you provide q-PCR data, raw value?

*We chose not to provide total miRNA expression raw values since only the relative expression values*

*could be used in the data analysis as described in the methods section (For further data analysis the*

*relative expression levels of miRNAs were calculated using the comparative delta Ct (threshold*

*Rebuttal letter*

*cycle number) method ( $2^{-\Delta\Delta Ct}$ ) implemented in the RT-PCR System software. The relative Ct for*

*cel-miRNA-39 was used as a control in the normalization of miRNA-126, miRNA-145 and miRNA-155 Ct).*

6. Please comment on the strength of the association of miR base on analysis.  
*The comment has been addressed in the text Results section.*

*MiRNA-126 and miRNA-145 expression had a moderate correlation with plaque tissue characteristics.*

7. Please comment on potential use of mirRNAs 126, 145 and 155 as plasma biomarker if the result are divergent from previous studies supporting them as artheroprotective.  
*The comment has been addressed in the discussion.*

*“Consequently inconsistency in our and previous study results indicate that further studies are needed to provide more evidence for these miRNAs and their role in plaque pathogenesis and their potential use as plaque vulnerability biomarkers.”*

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2<sup>nd</sup> editorial decision

11-dec-2019

Ref.: Ms. No. JCTRes-D-19-00023R1

Circulating plasma microRNA-126, -145 and -155 and their association with atherosclerotic plaque characteristics.

Journal of Clinical and Translational Research

Dear author(s),

Reviewers have submitted their critical appraisal of your paper. The reviewers' comments are appended below. Based on their comments and evaluation by the editorial board, your work was FOUND SUITABLE FOR PUBLICATION AFTER MINOR REVISION.

If you decide to revise the work, please itemize the reviewers' comments and provide a point-by-point response to every comment. An exemplary rebuttal letter can be found on at <http://www.jctres.com/en/author-guidelines/> under "Manuscript preparation." Also, please use the track changes function in the original document so that the reviewers can easily verify your responses.

Your revision is due by Jan 12, 2020.

To submit a revision, go to <https://www.editorialmanager.com/jctres/> and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely,

Michal Heger  
Editor-in-Chief  
Journal of Clinical and Translational Research

Reviewers' comments:

Dear authors, to ensure full transparency to fellow scientists and as part of the journal's policy, I would like to ask you to provide the raw data as an online data supplement. Once that has been submitted to the editorial office through editorial manager, I will accept your paper. Assuming this will not be a problem, I would like to congratulate you in advance for having this important work accepted.

All my best,

Michal.

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Author's rebuttal

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[evija.knoka@gmail.com](mailto:evija.knoka@gmail.com)

Riga, 15 December 2019

Re: revision No. JCTRes-D-19-00023R1

Dear Michal Heger,

Thank you for finding our paper "Circulating plasma microRNA-126, -145 and -155 and their association with atherosclerotic plaque characteristics." suitable for publication. We are grateful for

the reviewers comments and have addressed all comments using the track changes function in Word

(attached as supplementary material not for publication). Moreover, every modification or rebuttal

of the reviewer's comments is detailed per comment below in red italics.

On behalf of the authors, kindest regards,

Evija Knoka

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#### REVIEWER COMMENTS

Reviewer #1: Dear authors, to ensure full transparency to fellow scientists and as part of the journal's policy, I would like to ask you to provide the raw data as an online data supplement.

5. Will you provide q-PCR data, raw value?

*The q-PCR raw data has been added in table 1.*

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3<sup>rd</sup> editorial decision

15-dec-2019

Ref.: Ms. No. JCTRes-D-19-00023R2

Circulating plasma microRNA-126, -145 and -155 and their association with atherosclerotic plaque characteristics.

Journal of Clinical and Translational Research

Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly review for any errors.

Thank you for submitting your work to JCTR.

Kindest regards,

Michal Heger  
Editor-in-Chief  
Journal of Clinical and Translational Research

Comments from the editors and reviewers: