Author's response to reviews

**Title:** Association of iron overload based quantitative T2* MRI technique and carotid intima-media thickness in patients with beta-thalassemia: A cross-sectional study

**Authors:**

shahram akhlaghpour (akhlaghpour@nmri-ir.com)
morteza hoseini (m.hoseini11249@yahoo.com)
amirhosein jafarisepehr (dr-jafarisepehr@yahoo.com)

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**Author's response to reviews:** see over
Cover letter

Reviewer 1: ELISABETTA BIANCHINI

Discretionary revisions:

1) Page 9, “Carotid Ultrasound” section: please specify how IMT was assessed (was it measured automatically or manually)?
   
   **Answer:** IMT were measured manually and added in the text.

2) Page 9, “Carotid Ultrasound” section: specify ultrasound equipment setup during acquisition (i.e. gain, depth etc).
   
   **Answer:** The gain was at 60-70 dB that is usual in clinical practice and mentioned in the text.

3) Page 13, “Discussions” section: in the limitations also the relative low sample size should be included.
   
   **Answer:** This limitation was expressed and a non-parametric analysis was also added to decrease the effect of this limitation.

4) Table 3 should me made clearer (i.e. add the p values).
   
   **Answer:** Corrected and added to Table 3.

5) References regarding IMT might be substituted by more recent ones.
   
   **Answer:** New referenced were replaced in the text.

6) Tables’ labels should be reviewed.

   **Answer:** Revision was done.
Reviewer 2: Jerome Sullivan

No comments for authors.

Reviewer 3: Anna Södergren

Discretionary Revisions

Overall Answer:

All of the patients had been received chelation therapy with subcutaneous deferoxamine, but compliance to the chelation therapy was different in the patients and according to this compliance the patients had different iron load from normal to severe. We did not study about the direct effect of chelation therapy duration on IMT, because these data was not completely reliable. And the chelating effect was being on Iron load which we measured it directly.

Patients with hyperlipidemia were excluded from this study and LDL proposed as an important mediator in atherosclerosis process by other studies however as atherosclerosis is a multifactorial process, we tried to only assess the role of iron in this study.

Thalassemic patients have mostly blood lipid levels within the normal range and Prevalence of lipid and lipoprotein abnormalities is much lower as compared to the general population of the same age[34], but carotid IMT is significantly higher in thalassemic patients in comparison with the healthy persons[35]. This subject shows the important role of the body iron store in atherosclerosis process.

Minor essential revisions:
1- On page 9 line 5, I think there is a mistake: please correct “last 2 cm” to a more correct description

**Answer:** This item was corrected in the text and highlighted.

2- On page 10, line 7 and 13-14 the p-values are duplicated from the Tables. Data in tables should not be duplicated in the text.

**Answer:** The duplicated items were corrected in the text.

3-In Table 1: please give the body mass index instead of weight and height.

**Answer:** This item was corrected in the Table 1.

4-In Table 2: does the correlation with age include all patients, and is the age used as a continuous variable, or are the patients analyzed as groups as in Table 3?

**Answer:** The age used as a continuous variable, and mentioned in the text.

5-Figure 1 is not mentioned in the text, please correct this.

**Answer:** Corrected and highlighted.

**Major compulsory revisions:**

1-Thalassemic patients routinely were assessed for iron load with MRI once in year and patients in this study were referred from the hematology clinic for this routine checkup and this fact eliminate the selection bias towards a more severe disease.

2-The thalassemic patients in this study were relatively in lower age groups and had not previous history of CV events.
3-Because of the relatively low sample size in this study we also used from a non-parametric test (kruskal-wallis analysis). The result was the same and expressed in the text.

4-Discussion part was corrected about potential mechanisms and prevention of the development of atherosclerosis.

Duplicated parts in the discussion also were corrected.

5-We stated that our finding is in agreement with previous findings that expressed iron is the risk factor in atherosclerosis process but some studies could not find any association between iron and atherosclerosis process. Therefore this study designed to dissolve these discrepancies.