

Reply to the Reviewer code 03976790:

1. The aim of the study is stated in the paragraph titled "aim" in which the authors wrote: "A comprehensive search of English language articles was performed in the MEDLINE database without using other search filters except the publication interval between 2005 and 2020". It would be useful to clarify why the interval chosen was between 2005 and 2020.

The following sentence has been added: Before 2005 no papers regarding EndoPAT 2000 in pediatric endocrinological and metabolic diseases have been found.

2. The titles of parts need to be developed:- Page 7: for example: "aim of the review" instead of "aim".- Page 7: "DIABETES MELLITUS" could be: "study in pediatric patients with diabetes mellitus".- Page 10: METABOLIC SYNDROME could be : "study in patients with metabolic syndrome".- Page 13: "CANCER SURVIVORS" could be: "endothelial dysfunction in cancer survivors".

The text has been amended.

3. When an abbreviation is written for the first time in the text, give the complete name. Ex: page 7: BMI (body mass index); page 9: LDL (low density protein), CVD (cardio vascular disease); page 10: IR; page 12: HOMA-IR (Homeostatic model assessment of insulin resistance).

The complete name has been added before the abbreviations.

4. Page 9: "Pareyn et al.": number the reference; there are two references (51 and 59) in the reference list. Affect the reference (51, I suppose).

We confirm the reference number 51.

5. Page 10: "adipocytokine" instead "adypocytokine"

Amended.

6. Page 12: define "RH-PAT" (instead "PAT-RHI") at this page instead page 13.

Amended.

7. Page 13: remove "body mass index" and write "(BMI)" instead "body mass index (BMI)" (the abbreviation has already been defined)

Amended.

8. Figure 1: in the legend, is it "this value" or "these values"?

Amended as this value.

9. Tables 1, 2 and 3: number each reference in the table and check if they are present in the list of references.

The list of references has been included in each Table.

Reply to the Reviewer code 03659796:

1. Spelling mistake in title: the “impariment” should be “impairment”
Amended.
2. In the part of Conflict of interest, there is an incomplete word “interes” which should be “interest”
Amended.
3. What are the most important papers regarding ED detection mainly talked about? It is suggested to describe your main body of this review in brief and reduce introduction in your abstract.
The main body of the review has been included in the introduction, and the abstract introduction has been reduced.
4. The abstract part did not mention the headline CANCER SURVIVORS as well as ENDOTHELIAL IMPAIRMENT IN PITUITARY DYSFUNCTION. It is suggested to add relevant description.
These pathological conditions have been added in the abstract body.
5. The “are” in the sentence “The early damage negatively affects quality of life and are responsible for morbidity and mortality even at young age” should be “is”
Amended.
6. The references are recommended at the end of the part VASCULAR ENDOTHELIUM. Additionally, in the part of ED DETECTION, references are missed in the fourth paragraph. Please check the rest of the review.
Amended.
7. What’s the meaning of “Several serum inflammatory markers are available to detect ED, sometimes due to insulin resistance”? What is the relation between insulin resistance and the markers below? Are all of these markers increased in insulin resistance patients?
The following sentence has been added: Insulin resistance is associated by a global inflammatory status, characterized in the majority of cases by positivity of several inflammatory markers and is responsible for endothelial impairment leading to angiopathy. At present none of these markers has a prognostic value, and their use in clinical practice remains speculative.
8. The references are needed in the sentences “In particular... intra- and inter-subject”
Amended.
9. As described below, the study of reference no. 51 also had the conclusion of “RHI was significantly lower in patients group”, but was not included in the references of the conclusive words in the part DIABETES MELLITUS.
The text and reference number have been modified as follows: In 3/5 studies RHI was significantly lower in patients group^[48-50]; in particular, Pareyn et al reported a significantly lower RHI, especially in T1DM females^[50] Males had a lower BMI and were less sexually mature (3 males were prepubertal, while all the females were post-pubertal)^[50]. This might explain the difference reported since it has been described that prepubertal RHI is lower than in a mid-or late pubertal state^[44,45]. No other differences between males and females have been reported^[51].
10. What does this “they” refer to in “In 1/5 RHI was significantly lower in T1DM males than in females [50] They had a lower BMI and were less sexually mature”? The male patients or the female patients?].
Amended as In 1/5 RHI was significantly lower in T1DM males than in females^[51].
11. This study were not fit in your criteria of adolescent, but with detailed description with “An interesting study by Heier et al. ... did not correlate to RHI.”. What’s the significance of describing it? It is suggested to reduce content in this paragraph
The study has been described since it postulated that the cut off proposed might not be correct. Therefore, the paragraph has been shortened as suggested.
12. As described “Only two studies (not in table) reported “Time to peak” instead of RHI [68,71].”, Why were these two studies excluded? Please explain it concisely.
We excluded the study by Hudgins et al since peak response and/or area under the curve instead of RHI have been reported. By mistake, the reference #68 has been mentioned as not included in the table.
13. There are several spelling errors. The sentence “an excellent reproducibility” should be “excellent reproducibility”. The “T1D” in “In addition ... untreated group.” should be “T1DM”. And it should be

“resistance” in “In the study of Czipelova et al RHI was not influenced by BMI, but was related with systemic vascular resistances [66].” A space was missed in “In two studies ... age groups [67].” . There is an extra word in “Other authors ... endothelial function [73,74]. ” . The “that” should be “which” in “Moreover, RHI was negatively associated with augmentation index, that was higher in patients with NAFLD [75].” A space was missed in “triglycerides($p<0.04$)” .

All the spelling errors have been amended in the text.

We hope that these amendments will be in accordance to reviewers' requests.

Best regards

Giuseppe d'Annunzio