Author’s response to reviews

Title: Acute effect of healthy walking on arterial stiffness in patients with type 2 diabetes and differences by age and sex: a pre-post intervention study.

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Author’s response to reviews:

Dear Editor:

Thank you for your help in reviewing this manuscript with a view to considering its publication in the BMC Cardiovascular Disorders

Following the suggestions of the editor and the reviewers, we enclose a new version of our manuscript entitled: “Acute effect of healthy walking on arterial stiffness in patients with type 2 diabetes and differences by age and sex: a pre-post intervention study.” (Reference number BCAR-D-18-00376), together with our replies to all the issues raised.

We look forward to hearing from you. If you have any additional request or need any further information, please contact us.

Yours sincerely,

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TECHNICAL COMMENTS:

- The method section contains portions of text duplicated from previous publications. Please ensure that appropriate attribution to the original source is provided or the text re-written.

EDITOR COMMENTS:

BMC Cardiovascular Disorders operates a policy of open peer review, which means that you will be able to see the names of the reviewers who provided the reports via the online peer review system. We encourage you to also view the reports there, via the action links on the left-hand side of the page, to see the names of the reviewers.

MAIN CHANGES INTRODUCED

1) We have rewritten the methodology section to try to avoid text duplicated from previous publications.

2) We have modified the title of the manuscript.

3) We have added the analysis of the data by exercise intensity, as supplementary material.

REVIEWER #1 (Wilmer W. Nichols):

Authors' Answer

First, thank you for your work in reviewing this manuscript. Your contributions and suggestions will improve the understanding of the text.

1. On page 6 the authors say the study group included patients 25-75 years and they state it was 61.2-68.1. This is confusing.

Authors' Answer

This is a subanalysis of the intervention group, in 89 subjects with type 2 diabetes, aged between 40-70 years.

The values 61.2-68.1 represent the interquartile range (subjects between the 25th and 75th percentile).

The real range of our sample was 40-70 years. We have corrected this value in the manuscript:
This is a subanalysis of the intervention group to evaluate the response to healthy walking according to age and sex, in 89 subjects with type 2 diabetes, aged between 40-70 years.

The inclusion criteria were: patients with type 2 diabetes of both sexes, routinely monitored at the health care center, aged 40-70 years who, after receiving information about the study, agreed to take part and signed the informed consent.

2. Page 8, line 7, probable error ha should be ba

Authors' Answer

We have modified the equation in the manuscript:

Page 8 Line 174: The CAVI values were automatically calculated by estimating the stiffness parameter $\beta$ in the following equation: $\beta = 2\rho \times \frac{1}{(P_s - P_d)} \times \ln \left( \frac{P_s}{P_d} \right) \times \text{PWV}_2$, where $\rho$ is the blood density, $P_s$ and $P_d$ are SBP and DBP in mmHg, respectively, and the PWV is measured between the aortic valve and the ankle (considered a measure of central and peripheral arterial stiffness) $^1$.

3. On page 8 explain how baPWV could be measured from the aortic valve to the ankle. I not sure how accurate the equation is that is used to calculated baPWV.

Authors' Answer

We regret the error. The CAVI is a measure that evaluates central and peripheral arterial stiffness, however the baPWV measures the speed of the pulse wave from the brachial artery to the tibial artery, considering it a measure of peripheral stiffness.

We have correctly written this paragraph in the new manuscript, as shown below:

Page 8 Line 174: The CAVI values were automatically calculated by estimating the stiffness parameter $\beta$ in the following equation: $\beta = 2\rho \times \frac{1}{(P_s - P_d)} \times \ln \left( \frac{P_s}{P_d} \right) \times \text{PWV}_2$, where $\rho$ is the blood density, $P_s$ and $P_d$ are SBP and DBP in mmHg, respectively, and the PWV is measured between the aortic valve and the ankle (considered a measure of central and peripheral arterial stiffness) $^1$. The average coefficient of the variation of the CAVI is less than 5%, which is small enough for clinical use and confirms that the CAVI has favourable reproducibility $^2$. The baPWV was estimated using the following equation: $\text{ba-PWV} = \frac{(0.5934 \times \text{Height (cm)} + 14.4724)/\text{tba}}$, (tba is the time interval between the arm and ankle waves) (considered a measure of central and peripheral arterial stiffness) $^3$. The CAVI was classified as normal (CAVI <8), borderline (CAVI $\geq$8 or $<9$), or abnormal (CAVI $\geq$9). Abnormal CAVI represents subclinical atherosclerosis 4-6.
4. Page 12, in the group with more age......should be in the older group.

Authors' Answer

Following the suggestions of the reviewer, we have modified it by older group:

Page 12 Line 268: On the other hand, as in the classification by sex, in the lower extremities, there was a decrease in SBP and in the PP in both groups, but only there was a decline in DBP of -2.0 mmHg (95% CI: -3.3 mmHg to -0.7 mmHg), in the older group.

REVIEWER#2:

This is a generally well-written paper that looks at the effect of healthy walking on arterial stiffness. It appears to be an important topic, and the research question appears adequately addressed with the methodological approach. I have a few comments to improve the clarity of the manuscript, which I outline below.

Authors' Answer

First, thank you for your work in reviewing this manuscript. Your contributions and suggestions will improve the understanding of the text.

1. TITLE

1.1. It's good practice to include the study design in the title. I understand this paper is a sub-analysis of an RCT, but the design of the analysis was not randomised. Something should be included to give the reader an understanding as to the methodological approach.

Authors' Answer

Following the recommendations of the reviewer, we modified the title:

Page 1 Line 2: Acute effect of healthy walking on arterial stiffness in patients with type 2 diabetes and differences by age and sex: a pre-post intervention study.

2. INTRODUCTION

2.1. The aim probably needs some rewording. The authors aimed to "evaluate the acute effect", but without a randomised design it's not possible to achieve this aim. Would "association" work better?
Authors' Answer

Following the recommendations of the reviewer, we modified the aim throughout the study:

Page 3 Line 48: Our aim, therefore, is to evaluate the association between healthy walking and acute effects on the parameters of arterial stiffness in subjects with type 2 diabetes.

Page 6 Line 117: Therefore, this study aims to evaluate the association between healthy walking and the acute effect on the parameters of arterial stiffness in patients with type 2 diabetes and to analyse the differences for age and sex.

2.2. Do the authors mean "gender", or "sex"? I think they are referring to the latter.

Authors' Answer

To improve the understanding of the expression, we have changed the term gender by sex throughout the manuscript:

Page 1 Line 2: Acute effect of healthy walking on arterial stiffness in patients with type 2 diabetes and differences by age and sex: a pre-post intervention study.

Page 3 Line 53: This is a subanalysis of the intervention group to evaluate the response to the healthy walking according to age and sex, in 89 subjects with type 2 diabetes, aged between 40-70 years.

Page 5 Line 106: The findings on the acute effect of the exercise and its magnitude on BP are contradictory, presumably due to the differences in sex and age in the different studies 7.

Page 6 Line 115: However, there is less evidence of the acute effect of the exercise in subjects with diabetes, considering also subgroups of age and sex. Therefore, this study aims to evaluate the association between healthy walking and the acute effect on the parameters of arterial stiffness in patients with type 2 diabetes and to analyse the differences for age and sex.

Page 6 Line 126: This is a subanalysis of the intervention group to evaluate the response to the healthy walking according to age and sex.

Page 6 Line 134: The inclusion criteria were: patients with type 2 diabetes of both sexes, routinely monitored at the health care center, aged 40-70 years who, after receiving information about the study, agreed to take part and signed the informed consent. The inclusion criteria were: patients with type 2 diabetes of both sexes, routinely monitored in the health care center, from 40 to 70 years of age who, after receiving information about the study, agreed to participate and signed the informed consent.
Before performing the intervention, the sociodemographic and lifestyle variables were collected: age, sex, marital status, educational level and toxic habits (tobacco and alcohol consumption).

A logistic regression analysis was performed considering the CAVI and the ankle pulse pressure as dependent variables (reduction = 1, no reduction = 0) and as independent variables sex (male = 1, female = 0), physical activity (METs/min/week), DBP (mmHg), BMI (kg/m²), age (years), hypertension (hypertensive subject=1; non-hypertensive subject=0), dyslipidemia (dyslipidemic subject=1; non-dyslipidemic subject=0) and baseline CAVI value or baseline ankle pulse pressure value (mmHg).

Table 1 shows the characteristics (overall and by sex) of 89 patients with type 2 diabetes, with an average age of 65.0 years (61.2 – 68.1), of which 52.8% are hypertensive, 59.9% dyslipemic and 10.1% smokers.

The differences in the parameters before and after performing the healthy walking by sex are shown in Table 3.

On the other hand, as in the classification by sex, in the lower extremities, there was a decrease in SBP and in the PP in both groups, but only there was a decline in DBP of -2.0 mmHg (95% CI: -3.3 mmHg to -0.7 mmHg), in the older group.

In our study, the logistic regression shows that the only variable that could influence the change on the parameters of arterial stiffness after the healthy walking is sex.

Various studies have linked sex with differences in the CAVI, as occurs in our study, the CAVI being less in females than in males 9, 10, irrespective of their age.

3. METHODS

3.1. The sample size presented is one not related to the outcome of interest. Could the authors perform a post-hoc sample size calculation on the paper's current outcome so ensure that the analysis was adequately powered?

Authors' Answer

Following the recommendations of the reviewer we have included the post-hoc sample size calculation:
With the 89 subjects included, and considering an alpha risk of 0.05 and a common standard deviation of the CAVI of 1.25, our study would have a contrast power for paired groups of 0.62, to detect a difference as statistically significant between the pre-intervention measure (8.6) and the post-intervention (8.3), of 0.3 units.

3.2. How were the participants divided into different walking intensities? Was this random or was it based on ability, for example?

Authors' Answer

The groups were formed taking into account the walking ability of each subject. The subjects who had a greater capacity to carry out the exercise, made the walk in the group that walked at approximately 6 km/h, while the subjects who had less capacity did so at a speed of 3-4 km/h.

We cannot assure that these speeds were constant throughout the walk.

3.3. Could the authors comment on the extent to which measurement bias was reduced? e.g. were the CAVI examinations done by staff blinded to the aim of the study? Was is the same member of staff for each individual participant? How can validation be assured here?

Authors' Answer

Due to the nature of the intervention, the participants could not be blinded. However, the researcher who carried out the intervention in the study group was different from the person responsible for assessment and standardized counseling. The person responsible for carrying out the measurements before and after the intervention of all the participants was blinded to the objective of the study, to avoid bias. In addition, the person responsible for statistical analysis remained blinded throughout the study.

The measurements were carried out with Vasera VS-1500, which has already been validated previously. On the other hand, this device performs the measurement automatically, without there being variability between the people who perform the measurement.

We agree with the reviewer that this information is important for the manuscript. We have included the following paragraph:

Page 7 Line 148: Masking

Due to the nature of the intervention, the participants could not be blinded. However, the researcher who carried out the intervention in the study group was different from the person responsible for assessment and standardized counseling. The person responsible for carrying out the measurements before and after the intervention of all the participants was blinded to the
objective of the study, to avoid bias. In addition, the person responsible for statistical analysis remained blinded throughout the study.

3.4. It's not clear how the authors manipulated the CAVI/ankle pulse pressure to create a binary variable for the logistic regression analysis.

Authors' Answer

We assigned the value 1 when there was a reduction of the CAVI after the walk from baseline and 0 when there was no this reduction after the walk, as it is indicated in the section of statistical analysis.

3.5. It's also not clear how soon after the walking ended that post-intervention measurements were taken.

Authors' Answer

The post-intervention measures were taken immediately after the walk was completed. When the subjects arrived at the health center they went directly to the research unit and the measurement was made using the Vasera device VS-1500. After completing this test (5 min), capillary puncture was performed to determine blood glucose.

We have added this information in the manuscript:

Page 8 Line 166: To evaluate the acute effects of the healthy walking, the main study variables were measured before and immediately after it.

4. RESULTS

4.1. The authors have conducted a high number of statistical tests, and this increases the chances of false positives. Could the authors correct for multiple testing?

Authors' Answer

The reason we carry out these statistical tests is that our results are disaggregated by age and sex. In all the tests used, the Bonferroni correction was used to adjust the p-value.

We have added this information in the manuscript:

Page 10 Line 230: T-Student or U Mann-Whitney tests were accordingly used to test the relationship between quantitative variables with Bonferroni correction.
4.2. In Table 5, should the authors be adjusting for baseline CAVI/ankle pulse pressure values?

Authors' Answer

Following the recommendations of the reviewer, we have included the adjusted for baseline for CAVI and ankle pulse pressure values, being as follows in the manuscript:

Page 3 Line 64: It is observed that males have an OR of 2.981 (IC=95% 1.095 to 8.119) to achieve a reduction in the CAVI (p<0.05) and an OR of 2.433 (95%CI: 0.871 to 6.794) in the ankle PP (p>0.05), compared with females.

Page 4 Line 67: Conclusions: The findings of this study suggest that daily aerobic exercise at a low to moderate intensity, such as healthy walking, has an immediate beneficial effect on the cardio-ankle vascular index, especially in males.

Page 11 Line 235: A logistic regression analysis was performed considering the CAVI and the ankle pulse pressure as dependent variables (reduction = 1, no reduction = 0) and as independent variables sex (male = 1, female = 0), physical activity (METs/min/week), DBP (mmHg), BMI (kg/m2), age (years), hypertension (hypertensive subject=1; non-hypertensive subject=0), dyslipidemia (dyslipidemic subject=1; non-dyslipidemic subject=0) and baseline CAVI value or baseline ankle pulse pressure value (mmHg).

Page 12 Line 276: In the logistic regression analysis (Table 5), it can be seen that being male has an OR of 2.981 (95% CI: 1.095 to 8.119) to obtain a reduction in CAVI (p<0.05) and an OR of 2.433 (95% CI: 0.871 to 6.794) to obtain a decrease in the pulse pressure in the ankles (p>0.05), after the healthy walking, compared to being female.

Page 15 Line 338: The findings of this study suggest that daily aerobic exercise at a low to moderate intensity, such as healthy walking, has an immediate beneficial effect on the Cardio-ankle vascular index, in patients with type 2 diabetes, especially in males.

4.3. Why did the authors not consider analysing the data by exercise intensity?

Authors' Answer

Following the recommendations of the reviewer, we have included the analysis of the data by exercise intensity, as supplementary material (Table S1):

5. DISCUSSION

5.1. The authors should consider using more cautious language in their discussion - this was a pre-post intervention without a control group, and with probable Type 1 Errors - so causality cannot be reliably inferred.
Authors' Answer

Following the suggestion of the reviewer, we have modified the discussion section being as follows:

Page 13 Line 282: The main findings of the study were that the healthy walking of low-moderate intensity could have an immediate improvement of parameters of CAVI in patients with type 2 diabetes, especially in males and in people over than 65 years, since this is an inexpensive, simple and everyday exercise.

Various studies 11-13 support our results on the immediate beneficial effect that aerobic exercise could have on the parameters of arterial stiffness. Tabara et al. 14 found an association of the immediate effect of exercise with the long-term effects on parameters of arterial stiffness. Along these same lines, Madden et al. 15 found that aerobic training, on a treadmill and cycle ergometer, for 3 months produced an improvement in the arterial stiffness, despite not finding any improvement in other parameters such as weight, BP, BMI and waist-to-hip ratio. Yokoyama et al. 16 conducted a 3-week study, combining exercises on an ergometer and walking, which also found a decrease in arterial stiffness.

The intensity and type of exercise deserve key consideration when investigating the effect of exercise on arterial stiffness. Thus, in the study carried out by McClean et al. 17, they found that no change had taken place in the parameters of arterial stiffness, since the intensity of the aerobic exercise had been insufficient. However, Wang et al. 13 found that low to moderate intensity aerobic exercise such as the healthy walking carried out in our study, produces a transient improvement in arterial stiffness, these results being supported by the meta-analysis performed by Ashor et al. 11.

In our study, the logistic regression shows that the only variable that could influence the change on the parameters of arterial stiffness after the healthy walking is sex; it being found that males are more than twice as likely as females to reduce the CAVI, compared to baseline, after the healthy walking. Some in vitro studies have described the action of oestrogen on the vessels, in the reduction of smooth muscle proliferation 18 and in the increase in the release of nitrous oxide that leads to vasodilation 19. Although the females studied are of an advanced age, and it can be assumed that they are in the post-menopausal state, there is evidence to suggest that differences due to sex in vascular biology are related not only to the type and levels of sex hormones, but also with the differences in the cells and in the tissues responsible for the responses to different stimuli 8. Various studies have linked sex with differences in the CAVI, as occurs in our study, the CAVI being less in females than in males 9, 10, irrespective of their age.

Regarding the blood pressure, there was a decrease in both SBP and DBP in both lower extremities. These results are consistent with the meta-analysis conducted by Carpio et al. 7, where a reduction of 3 to 4 mmHg was found, confirming the importance of the immediate effect of exercise as a non-pharmacological method in reducing BP.

Considering the possible association, of the healthy walking used in our study, with the immediate beneficial effects on the CAVI, blood glucose and BP in the both lower extremities,
this could be an activity to be recommended at primary care consultations, especially in males and in people over than 65 years, since this is an inexpensive, simple and everyday exercise. There was no improvement of BP in the upper extremities, this being because healthy walking exercise the both low extremities more intensely, furthermore, these are subjects with type 2 diabetes, a population more likely to have peripheral artery disease that causes a decrease in BP only in both lower extremities, after the exercise. We therefore believe that more studies are required to establish which exercises can be added to the healthy walking to produce cardiovascular improvement in both the upper and lower limbs.

This study has various limitations that need to be considered in the interpretation of our results. Firstly, the patients with diabetes included had multiple pathologies, and may be being treated with various drugs, which could modify the CAVI and BP values. We have tried to control this limitation through the inclusion of the most common drugs in the logistic regression. Secondly, being a pre-post intervention study, we had no control group with which to compare the data. Finally, the small size of the sample can make it difficult to find differences caused by the exercise.


