PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Evolution of target organ damage and hemodynamic parameters over 4 years in patients with increased insulin resistance. The LOD-DIABETES prospective observational study.
AUTHORS	Gomez-Marcos, Manuel; Recio-Rodriguez, Jose; Patino-Alonso, Maria; Agudo-Conde, Cristina; Rodriguez-Sanchez, Emiliano; Maderuelo-Fernandez, Jose; Gomez-Sanchez, Leticia; Gomez-Sanchez, Marta; Garcia-Ortiz, Luis

VERSION 1 - REVIEW

REVIEWER	Paolo Melillo Second University of Naples
REVIEW RETURNED	27-Nov-2015

GENERAL COMMENTS	I read with interest the manuscript "Evolution of target organ damage and hemodynamic parameters over 4 years in patients with increased insulin resistance. The LOD-DIABETES trial" It describes the results of a longitudinal study evalatuating target organ damage and hemodynamic parameters in patients suffering from Type 2 diabetes mellitus and from metaboloc syndrom. The main concern is related to the influence of age in the findings of the study. The two groups, as the authors stated in the study limitation discussion, were different for age and this could influence the results. I recommend to review the statistical analysis by adopting a regression model, in order to explore progression of the parameters over follow-up, by adding as covariate the baseline age, and as factor the disease (diabete versus metabolic syndrom). Moreover, the progression of the parameters may be not appropriately described by a linear model, for example, an exponential model could fit better. Moreover, the statistical analysis plan may impact the study design. For example, age-matched groups would have avoided the influence of age.

REVIEWER	Toshinoi Yuasa Graduate School of Medical and Dental Sciences, Kagoshima University, Japan
REVIEW RETURNED	01-Dec-2015

GENERAL COMMENTS	Authors may would like to reveal the the evolution in the cardiac, renal and vascular TOD in type 2 DM and MetS and the difference between themselves. Remarkable point in the current paper is that authors show the differences of lots of parameters progression including IMT and PWV between 2 groups prospectively and during

	relatively long time. I have some revisions as described below. 1)Page 7 and 8: Authors should be the criteria of TOD IMT and TOD ABI clearly as well as PWV in text. And I was not able to find the criteria of “vascular TOD”. Would you please make sure again? 2)Page 9, line 11: Please demonstrate the criteria of “TOD Heart” concretely as well as other TOD. 3)Figure 3, figure legend: “Figure 3a and 3b” and “figure 3c and 3d” is correct? Maybe, I think “figure 3a and 3c” and “figure 3b and 3d” Would you check it again? 4)Page 11, in result: Finally, the current data show that %TOD vascular, %TOD IMT and %TOD cf PWV in type 2 diabetes increased significantly after 4 year follow-up. But, the value of IMT and PWV had no significant changes after adjusting for age, gender, mean BP, etc. You show the p value of IMT (p=0.909) in page 11, line 11. Is this correct? Because figure 3b show IMT after adjusted still looks maintain the increment of IMT after 4 year follow-up. I think you should add the standard deviation to the each values in all figures. 5)Abstract, line 11: The parentheses are used doubly. Please check it. Page 5, line 1: The letters of “The purpose” should not be bold. Page 6, line 4: “MEASUREMENT:” should be “Measurement:” Page 6, line 16, 22, Page 7, line 11: Authors can cut full terms of PWV, PAIx and CAIx. Authors already show abbreviations in page 6, line13-14.

REVIEWER	Joshua Barzilay Kaiser Permanente of Georgia 3650 Steve Reynolds Blvd Duluth GA 30096 USA
REVIEW RETURNED	04-Dec-2015

GENERAL COMMENTS	The authors of this study examine a cohort of people with T2DM and MetS to examine the progression/or lack of progression of vascular disease markers. There is data of interest here but I believe the authors have "missed the mark" and have not clearly defined what they are looking for. What they are really doing is examining the degree of progression of vascular disease markers in people with T2DM and MetS and seeing if the milieu in each condition leads to the same or different outcomes. MetS is"insulin resistance", while T2DM is "hyperglycemia and insulin resistance." They have to define this as the question that they are examining and to fashion their DISCUSSION around this issue. In other words - what is the effect of raised sugar on vascular disease markers as compared to insulin resistance alone? This is not done. Instead the authors compare their results one by one to other studies. This offers no coherent message and makes for confused reading. Please see the article by Barzilay et al in Diabetes Care. 2001 Jul;24(7):1233-39 for guidance. Also why are you showing all kinds of statistics for an observational study????????

VERSION 1 – AUTHOR RESPONSE

1) Reviewer: 1 Paolo Melillo Second University of Naples Please leave your comments for the authors below
"Evolution of target organ damage and hemodynamic parameters over 4 years in patients with increased insulin resistance. The LOD-DIABETES trial"
It describes the results of a longitudinal study evalatuating target organ damage and hemodynamic parameters in patients suffering from Type 2 diabetes mellitus and from metabolic syndrom.
The main concern is related to the influence of age in the findings of the study. The two groups, as the authors stated in the study limitation discussion, were different for age and this could influence the results. I recommend to review the statistical analysis by adopting a regression model, in order to explore progression of the parameters over follow-up, by adding as covariate the baseline age, and as factor the disease (diabetes versus metabolic syndrom). Moreover, the progression of the parameters may be not appropriately described by a linear model, for example, an exponential model could fit better. Moreover, the statistical analysis plan may impact the study design. For example, age-matched groups would have avoided the influence of age.

Authors' Answer
As discussed by the reviewer, one of the study limitations is the age difference between groups. To reduce its effect, we have included this variable together with gender, mean blood pressure and atherogenic index as adjustment covariates. However, as proposed by the reviewer, we have performed the regression model, including the age at baseline as a covariate, and the disease as a factor (diabetes versus metabolic syndrome). The results can be seen in the following figure.

Estimated unadjusted means (figure 3 a and 3 b), adjusted by age, of intima-media thickness (IMT) and pulse wave velocity (PWV) in type 2 diabetes and in metabolic syndrome patients.

These results are very similar to those shown in Figure 3 of the manuscript, adjusted for gender, mean blood pressure and atherogenic index.
However, if considered necessary, these results adjusted just for age may be added to the manuscript or published as supplemental material.
We agree with you when saying that this would have been avoided if we had taken it into account in the design.
Finally, we have analyzed the model that better reflects the variables analyzed. The following tables show the adaptation of the different models to the main variables (Tables 1a and 1b).
Table 1a: IMT
Origen IMT F Sig.
IMT Lineal 0.186 0.667
Quadratic 0.066 0.798
Cúbic 0.185 0.668
IMT * Group Lineal 8.137 0.005
Quadratic 3.558 0.062
Cúbic 0.601 0.440
Group: 0= Metabolic Syndrome; 1 = Type 2 diabetes

Table 1b: PWV
Origen PWV F Sig.
PWV Lineal 0.281 0.597

Quadratic 2.354 0.128
Cúbic 1.517 0.221
PWV * Group Lineal 3.565 0.062
Quadratic 2.647 0.107
Cúbic 2.744 0.101
Group: 0= Metabolic Syndrome; 1 = Type 2 diabetes

In order to give clarity to the results, we have modified and expanded the wording of the last paragraph in the Results section, remaining now as follows:

In the unadjusted repeated measures analyses, we found differences in IMT (p = 0.002), but not in the PWV (p = 0.709; Figure 3). After adjusting for age, gender, mean blood pressure and atherogenic index, the differences in the four-year of follow-up of the IMT disappear (p = 0.909), but did not modify the PWV (p = 0.223). An interaction effect is observed between the IMT*group (p=0.004) and the PWV*group (p=0.033), thus, from the third year, both IMT and PWV are higher in subjects with type 2 diabetes than in those with metabolic syndrome (Figure 3). However, in the post hoc contrasts, statistical significance (p≤0.01) is only reached in the first case. (Page: 11; Line: 15).

Reviewer: 2 Toshinoi Yuasa Graduate School of Medical and Dental Sciences, Kagoshima University, Japan
Please leave your comments for the authors below
Authors may would like to reveal the evolution in the cardiac, renal and vascular TOD in type 2 DM and MetS and the difference between themselves. Remarkable point in the current paper is that authors show the differences of lots of parameters progression including IMT and PWV between 2 groups prospectively and during relatively long time. I have some revisions as described below.
1) Page 7 and 8: Authors should be the criteria of TOD IMT and TOD ABI clearly as well as PWV in text. And I was not able to find the criteria of “vascular TOD”. Would you please make sure again?
2) Page 9, line 11: Please demonstrate the criteria of “TOD Heart” concretely as well as other TOD.

Authors' Answer
We have made the changes suggested by the reviewer and corrected the existing mistakes. In the Methods section, in the last paragraph of each measurement made, we have specified the criteria used to define target organ damage:

Intima media thickness: We considered TOD if IMT mean was > 0.90 mm or if there were atherosclerotic plaques with a diameter of 1.5 mm or a focal increase of 0.5 mm or 50% of the adjacent IMT.1 (Page: 8; Line: 10).

Pulse Wave Velocity: We considered TOD if the PWV was higher than 12 m/sec. 1. (Page: 6; Line: 21).

An ABI < 0.9 was considered TOD peripheral artery. 2 (Page: 8; Line: 24).

The TOD Heart was defined according to the 2013 European Society of Hypertension/European Society of Cardiology Guidelines criteria (Sokolow-Lyon index (SV1 + RV5 >3.5 mV), the modified Sokolow-Lyon index (largest S-wave + largest R-wave >3.5 mV), or Cornell voltage QRS duration product (>2440 mV*ms). 1 (Page: 9; Line: 13).

3) Figure 3, figure legend: “Figure 3a and 3b” and “figure 3c and 3d” is correct? Maybe, I think “figure 3a and 3c” and “figure 3b and 3d” Would you check it again?

Authors' Answer
We have corrected the mistake, and the figure legend is now as follows:
Figure 3. Estimated unadjusted means (figure 3a and 3c), and adjusted by age, gender, atherogenic index and office blood pressure (figure 3b and 3d) of intima-media thickness (IMT) and pulse wave velocity (PWV) in type 2 diabetes and in metabolic syndrome patients. (Page: 23; Line: 1).

Page 11, in result: Finally, the current data show that %TOD vascular, %TOD IMT and %TOD cf PWV in type 2 diabetes increased significantly after 4 year follow-up. But, the value of IMT and PWV had no significant changes after adjusting for age, gender, mean BP, etc. You show the p value of IMT (p=0.909) in page 11, line 11. Is this correct? Because figure 3b show IMT after adjusted still looks maintain the increment of IMT after 4 year follow-up. I think you should add the standard deviation to the each values in all figures.

Authors' Answer
We have reviewed the analysis and the values shown in the manuscript are correct.
We have modified the figure and included the standard error bars as shown in Figure 2, at the end of this document.

4) Abstract, line 11: The parentheses are used doubly. Please check it.
Page 5, line 1: The letters of “The purpose” should not be bold.
Page 6, line 4: “MEASUREMENT:” should be “Measurement:”
Page 6, line 16, 22, Page 7, line 11: Authors can cut full terms of PWV, PAIx and CAIx. Authors already show abbreviations in page 6, line13-14.

Authors' Answer
We have made all the changes suggested by the reviewer.

Reviewer: 3 Joshua Barzilay Kaiser Permanente of Georgia
Please leave your comments for the authors below
The authors of this study examine a cohort of people with T2DM and MetS to examine the progression/or lack of progression of vascular disease markers. There is data of interest here but I believe the authors have "missed the mark" and have not clearly defined what they are looking for.
What they are really doing is examining the degree of progression of vascular disease markers in people with T2DM and MetS and seeing if the milieu in each condition leads to the same or different outcomes. MetSis"insulin resistance", while T2DM is "hyperglycemia and insulin resistance." They have to define this as the question that they are examining and to fashion their DISCUSSION around this issue. In other words - what is the effect of raised sugar on vascular disease markers as compared to insulin resistance alone? This is not done. Instead the authors compare their results one by one to other studies. This offers no coherent message and makes for confused reading.
Please see the article by Barzilay et al in Diabetes Care. 2001 Jul;24(7):1233-39 for guidance.
Also why are you showing all kinds of statistics for an observational study????????

Authors' Answer
According to the recommendations of the reviewer, we have made the following changes in

the manuscript:
The purpose of this study was to evaluate the evolution of the cardiac, renal and vascular TOD and the hemodynamic parameters in patients with type 2 diabetes or metabolic syndrome (MetS) over four years of follow-up, as well as to analyze the differences between both groups. (Page: 2; Line: 6 and Page: 5; Line: 4).

Results:
We have reworded and extended the last paragraph in the Results section, now remaining as follows:

In the unadjusted repeated measures analyses, we found differences in IMT ($p = 0.002$), but not in the PWV ($p = 0.709$; Figure 3). After adjusting for age, gender, mean blood pressure and atherogenic index, the differences in the four-year of follow-up of the IMT disappear ($p = 0.909$), but did not modify the PWV ($p = 0.223$). An interaction effect is observed between the IMT*group ($p=0.004$) and the PWV*group ($p=0.033$), thus, from the third year, both IMT and PWV are higher in subjects with type 2 diabetes than in those with metabolic syndrome (Figure 3). However, in the post hoc contrasts, statistical significance ($p\leq0.01$) is only reached in the first case. (Page: 15; Line: 11)

Discussion:
Unlike previous studies that have examined the prevalence of cardiovascular diseases in relation to glucose disorders, in this study we have analyzed the difference between patients with type 2 diabetes or with MetS, in the evolution of vascular, renal and cardiac TOD. This study included a 4-year follow-up period of patients with type 2 diabetes or with MetS, and it showed an increase of carotid IMT and PWV TOD higher in type 2 diabetes than MetS. There were not significant differences in the frequency of renal and cardiac TOD in type 2 diabetes. Subjects with MetS have not any significant increase of TOD. Taken together, these results are consistent with the hypothesis that factors associated with glucose disorders promote atherosclerosis. In subjects with type 2 diabetes, the evolution of subclinical cardiovascular diseases is worse than in those with only an increased resistance to insulin without changes in blood sugar levels, as happens in patients with MetS.3 (Page: 11; Line: 28)
The evolution of vascular parameters (IMT and PWV over time) is a controversial matter, probably due to the control of cardiovascular risk factors and the influence of the drugs used in its control. (Page: 12; Line: 8)
Therefore, while the meta-analysis of Lorenz MW et al. (based on 1339 strokes from 16 studies) concluded that the association between IMT progression evaluated with ultrasounds, cardiovascular risk and the risk of subsequent cardiovascular events in the general population remains unproven. 4 In subjects with type 2 diabetes, conducted an intensive intervention on different cardiovascular risk factors over two years and managed to reduce the IMT, but none of the markers including endothelial function parameters, were useful in predicting such changes. 5 (Page: 12; Line: 11)
In contrast to these results, the Multi Ethnic Study of Atherosclerosis (based on 42 strokes) had a significant and positive association between yearly mean IMT progression and risk of stroke, 6 and another study concluded that rapid progression of IMT was associated with adverse cardiovascular outcome.7 The Tromsø study had higher levels of IMT at follow up in subjects with Mets than those without MetS. 8 MetS predicted IMT progression in people 50 years of age and younger, but not in other age groups, which indicated that MetS may be involved in the initiation of the atherosclerotic process, and in the European Lacidipine Study on Atherosclerosis (ELSA), 9 IMT progression was slightly greater in patients with MetS, but this was not significant after adjusting for other cardiovascular risk factors. Only type 2 diabetes patients showed increases in PWV ≥ 12 m / sec during the monitoring period. (Page: 12; Line: 18)

Previous studies have shown that clinical heart disease is more common in diabetics than in subjects with only an increased resistance to insulin and in diabetic women than in diabetic men.10 11 Our results contribute to these findings demonstrating that women with diabetes show a higher annual progression of IMT and PWV than diabetic men. This could explain the higher increase in the prevalence of cardiovascular diseases, as well as their higher severity in diabetic women. 10 11 (Page: 12; Line: 29)

Our findings suggest that patients with increased insulin resistance did not have differences in CAIx and PAIx. These results are consistent with previously published 12data in a Chinese population. 12 13. The behavior of ABI was similar in both patient groups, both in terms of absolute ABI values and the percentage of patients with ABI<0.9. Similar data have been published in other studies with patients with type 2 diabetes. 14 15 16. However, it must be remembered that in diabetic patients the standard threshold sensitivity (0.9) is lower and thus the efficiency of ABI is limited. (Page: 14; Line: 10)

This study has some limitations that must be considered. First, the number of subjects per group limits the power of analysis. Furthermore, these patients were not randomized, but involved consecutive sampling. The two groups are not fully balanced in terms of age (4 years of difference), which may influence the course. Remarkable point in the current paper is that this study shows the differences of lots of parameters progression including IMT and PWV between 2 groups prospectively for four years. (Page: 11; Line: 17)

This prospective study showed that the evolution of vascular TOD is different in subjects with type 2 diabetes respect to those with MetS. While IMT and PWV increased in type 2 diabetes, especially in diabetic women, these were not modified in MetS. The renal and cardiac TOD evolution, as well as the PAIx and CAIx, did not change in either group. (Page: 14; Line: 23)

VERSION 2 – REVIEW

REVIEWER	Paolo Melillo Second University of Naples
REVIEW RETURNED	13-Feb-2016

GENERAL COMMENTS	The authors addressed satisfactorily all the issues arisen in the peer review process

REVIEWER	Joshua Barzilay Kaiser Permanente of Georgia
REVIEW RETURNED	28-Jan-2016

GENERAL COMMENTS	The paper is improved as it now is focused on a specific question. What needs to be improved is the INTRO and DISC The INTRO is non-specific and does not get to the point. Consider: "MetS and T2DM are conditions characterized by insulin resistance. T2DM is further charaterized by increased glucose levels. Both conditions are strongly associated with vascular disease through risk factors that associate with IR, such as HTN, increased lipid levels, and increased inflammation levels. The individual role of elevated glucose levels in the development of vascular disease, independent of the other vascular risk factors, is uncertain. In the current study we examine a cohort with IR - one with MetS only, the other with T2DM. We examine prospectively the impact of T2DM compared to MetS on the development of vascular disease over 4 years as determined by anatomic and functional markers of vascular disease.

	By comparing the vascular outcomes of the two disorders we seek to determine the independent effect of elevated glucose levels on vascular disease." This kind of an INTRO is short and to the point and explains what you are trying to accomplish. Feel free to use it or not. I am just suggesting a way to make your objective clearer..... The same holds for the ABSTRACT, which is not organized well. 2. I would drop renal disease as an outcome. Renal disease develops very slowly over 10-20 years and it is unlikely to change in 3-4 years. Concentrate on vascular disease. You might want to adjust your analyses for renal disease as a covariate. 3. RESULTS - In Subjects with MetS..." something is missing near the "ABI" part of the sentence. 4. DISC - 1st paragraph - the sentence "In subjects with..." repeats the prior sentence - it can be dropped. 5. DISC - paragraph "In contrast to these results..." The first sentence discusses IMT and stroke. That is not germane to the paper which examines progression of IMT not vascular outcomes. Please delete.... Likewise delete the paragraph "Previous studies have shown.." for the same reason. 6. An English editor will need to fix the language. This is not a critique since it is hard to write in a non-native language, but needs to be done

VERSION 2 – AUTHOR RESPONSE

Reviewer: Joshua Barzilay Kaiser Permanente of Georgia
The paper is improved as it now is focused on a specific question. What needs to be improved is the INTRO and DISC
The INTRO is non-specific and does not get to the point. Consider: "MetS and T2DM are conditions characterized by insulin resistance. T2DM is further charaterized by increased glucose levels. Both conditions are strongly associated with vascular disease through risk factors that associate with IR, such as HTN, increased lipid levels, and increased inflammation levels. The individual role of elevated glucose levels in the development of vascular disease, independent of the other vascular risk factors, is uncertain. In the current study we examine a cohort with insulin resistance - one with MetS only, the other with T2DM. We examine prospectively the impact of T2DM compared to MetS on the development of vascular disease over 4 years as determined by anatomic and functional markers of vascular disease. By comparing the vascular outcomes of the two disorders we seek to determine the independent effect of elevated glucose levels on vascular disease. "This kind of an INTRO is short and to the point and explains what you are trying to accomplish. Feel free to use it or not. I am just suggesting a way to make your objective clearer. The same holds for the ABSTRACT, which is not organized well.
Authors' Answer
Following the recommendations of the reviewer, we have made the following changes in the manuscript:
ABSTRACT
We changed the first paragraph.
We examine prospectively the impact of type 2 diabetes compared to MetS on the development of vascular disease over 4 years as determined by anatomic and functional markers of vascular disease. By comparing the vascular outcomes of the two disorders we seek to determine the independent effect of elevated glucose levels on vascular disease.

In the methods subsection, we have deleted some wording: (Cornell voltage-duration product and Sokolow) and (creatinine, glomerular filtration and albumin/creatinine index).
INTRODUCTION
Cardiovascular disease morbidity-mortality is greater in people with type 2 diabetes or metabolic syndrome (MetS). 1 2 MetS and type 2 diabetes are conditions characterized by insulin resistance. Type 2 diabetes is further characterized by increased glucose levels. Both conditions are strongly associated with vascular disease through risk factors that associate with insulin resistance, such as hypertension, increased lipid levels, and increased inflammation levels.3-7 The presence of target organ damage (TOD) vascular 8-11, cardiac 12 and renal 13 14 increases the risk of cardiovascular complications independently of the existing estimated risk.
The individual role of elevated glucose levels in the development of vascular disease, independent of the other vascular risk factors, is uncertain. In the current study we examine a cohort with insulin resistance - one with MetS only, the other with type 2 diabetes.
We examine prospectively the impact of type 2 diabetes compared to MetS on the development of vascular disease over 4 years as determined by anatomic and functional markers of vascular disease. By comparing the vascular outcomes of the two disorders we seek to determine the independent effect of elevated glucose levels on vascular disease.
RESULTS
We have deleted the following sentence: There were no differences in renal or cardiac TOD

2. I would drop renal disease as an outcome. Renal disease develops very slowly over 10-20 years and it is unlikely to change in 3-4 years. Concentrate on vascular disease. You might want to adjust your analyses for renal disease as a covariate.
Authors' Answer
We have used the estimated glomerular filtration rate (eGFR) as an adjustement covariable in the repeated measures analysis and no change has been shown in the results. After adjusting for age, gender, office mean blood pressure, atherogenic index, and eGFR estimated according to CKDEPI formula, no differences have been found in either IMT ($p = 0.866$) or PWV ($p = 0.989$) in the four years of follow up.

3. RESULTS - In Subjects with MetS..." something is missing near the "ABI" part of the sentence.
Authors' Answer
We have modified the wording of this paragraph, as well as the previous one, remaining now as follows:
In subjects with type 2 diabetes, we observed an increase in IMT, in the percentage of subjects presenting plaques and the percentage of subjects with IMT> 0.9 mm in the follow-up. There were also changes in the ABI ($p< 0.01$) and in the Sokolow criteria.
Likewise, in subjects with MetS there were changes in the number of subjects with mean maximum IMT > 0.9 mm and the percentage of subjects with plaques ($p = 0.014$). There were also changes in the ABI ($p = 0.006$), in the Sokolow and in Cornell PDV criteria.

4. DISCUSSION - 1st paragraph - the sentence "In subjects with..." repeats the prior sentence - it can be dropped.
Authors' Answer
Following the recommendations of the reviewer, we have deleted the repeated paragraph. Now, it remains as follows:
Unlike previous studies that have examined the prevalence of cardiovascular diseases in relation to glucose disorders, in this study we have analyzed the difference between patients with type 2 diabetes or with MetS, in the evolution of vascular, renal and cardiac TOD. This study included a 4-year follow-up period of patients with type 2 diabetes or with MetS, and it showed an increase of carotid IMT and PWV TOD higher in type 2 diabetes than MetS. There were not significant differences in the frequency of renal and cardiac TOD in type 2 Diabetes. Subjects with MetS have not any

significant increase of TOD. Taken together, these results are consistent with the hypothesis that factors associated with glucose disorders promote atherosclerosis. In diabetics the evolution of subclinical cardiovascular diseases is worse than in those with only an increased resistance to insulin without changes in blood sugar levels, as happens in patients with MetS.3

5. DISCUSSION - paragraph "In contrast to these results..." The first sentence discusses IMT and stroke. That is not germane to the paper which examines progression of IMT not vascular outcomes. Please delete.... Likewise delete the paragraph "Previous studies have shown.." for the same reason.
Authors' Answer
Following the recommendations of the reviewer, we have deleted the two paragraphs suggested in the Discussion section. Now it remains the following paragraph:
The results show that women with type 2 diabetes mellitus present a higher annual progression of IMT and PWV than diabetic men. This could explain the higher increase in the prevalence of cardiovascular diseases, as well as their higher severity in diabetic women. 16 17

6. An English editor will need to fix the language. This is not a critique since it is hard to write in a non-native language, but needs to be done
Authors' Answer
The manuscript has been fully edited by American Manuscript Editors.
Attached is the editorial certificate.

VERSION 3 - REVIEW

REVIEWER	Joshua Barzilay 3650 Steve Reynolds Blvd Duluth GA 30096 USA
REVIEW RETURNED	16-Mar-2016

GENERAL COMMENTS	The paper is clearer now. A few small points 1. Diabetic is an adjective. Use diabetic person or diabetic people 2. You mention women have more vascular progression. This is not a study aim nor do you discuss it. Delete. 3. Page 10 - people evolved DM over 9 years. Generally people do not give exact numbers, Just estimates. 4. Page 11, lines 45 ff- says little. Delete

VERSION 3 – AUTHOR RESPONSE

Reviewer: Joshua Barzilay Kaiser
1. Diabetic is an adjective. Use diabetic person or diabetic people
Authors' Answer
Following the recommendations of the reviewer, we have replaced diabetic by diabetic people or diabetic person in throughout the manuscript.

2. You mention women have more vascular progression. This is not a study aim nor do you discuss it. Delete.
Authors' Answer
Following the recommendations of the reviewer, we have deleted the paragraph women have more vascular progression of the manuscript:

3. Page 10 - people evolved DM over 9 years. Generally people do not give exact numbers, Just estimates.
Authors' Answer
We reworded the evolution of diabetes type 2 that was over 9 years

4. Page 11, lines 45 ff- says little. Delete
Authors' Answer
Following the recommendations of the reviewer, we have deleted the paragraph these results are consistent with the hypothesis that the factors associated with glucose disorders promote atherosclerosis.