**Author’s response to reviews**

**Title:** Profile and Factors Associated with Glycaemic Control of Patients with Type 2 Diabetes in Greece: Results from the Diabetes Registry

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**Author’s response to reviews:**

June 26, 2019

Dear Prof Alexander Kokkinos,

Thank you very much for your letter informing us that our article is potentially acceptable for publication in BMC Endocrine Disorders. We are very grateful to you and the reviewers for the valuable suggestions on our manuscript "BMC Endocrine Disorders Profile and Factors Associated with Glycaemic Control of T2DM Patients in Greece: Results from the Diabetes Registry" [BEND-D-19-00159]. Our revisions have addressed all comments and incorporated all recommendations made by the reviewers. Changes were made using track changes.
All authors have read and approved the revised manuscript, and there are no financial or other relations that could lead to a conflict of interest.

Thank you in advance for your consideration.

On behalf of the authors,

Kyriakos Souliotis

Response to reviewers

Dear reviewers,

We would like to thank for your time and your valuable comments and suggestions. All of them were taken into consideration while preparing the revised version of the manuscript. Below please find our detailed responses to your comments.

Stavros Liatis (Reviewer 1)

1. The study is described as "prospective". However, although the data have been prospectively collected (during one year), the analysis is purely cross-sectional. Please replace "prospective" by "cross-sectional" throughout the manuscript.

Changes were made throughout the manuscript following reviewer’s comment.

2. Due to the cross-sectional nature of the analysis the term "predictor" is strongly discouraged. I suggest to use "associations" instead.

We would like to thank the reviewer for his suggestion, changes were made in text.

3. The data collection methodology is described as part of a diabetes registry creation. As registries are systems created to organize clinical information related to individual patients and populations, could the authors be more specific about this organization? How was this registry created and how were the participating centres selected?

The Diabetes Registry was developed through a collaboration of the University of Peloponnese and the Medical School of the University of Athens. The research tool used was developed on the basis of international best practice, published, disease risk indices [1,2] as validated by expert clinicians on the field. Participating centers were chosen as follows: out of 13 operating specialized diabetes centers in Attica, Piraeus, Macedonia and Thrace regions [3], 6 were contacted based on their special interest in diabetes research and their large geographic population coverage. 5 out of 6 participated in the study. A more detail presentation of the development of the registry is now added (page 7, lines 6-10; page 8, lines 1-5).
4. How was family history of diabetes defined (first degree, first and second degree)?

First degree of family history was taken into account. More specifically a patient was defined as having family history of diabetes if one or both of his/her parents or and any of his/her siblings were diagnosed with T2DM, at any time in the past. A sentence explaining how family history was defined is now added in the text (page 8, lines 16-18).

5. How were dietary factors and physical activity assessed? Were there validated questionnaires used? Why were only a few parameters of the diet presented and how/why have they been selected?

These dietary and physical activity factors were selected from the Diabetes Prevention toolkit [1,2]. Item selection was based on their clinical importance for the pertinent disease category, as defined by the clinical experts who collaborated in the development of the registry.

The pertinent paragraph has also been added in the main text (page 9, lines 16-20).

6. According to the figures presented in tables 1-4, there are missing data regarding several parameters (eg, educational level is reported in about half of the cases). Although the study population is consisted of 1141 individuals, the analysis related to glycemic control achievement is performed on 686 patients. Apart from the 106 patients excluded due to recent diagnosis of diabetes, other reasons of exclusion should also be explained.

First of all, we would like to thank the reviewer for his very useful comment. In many cases, patients were reluctant to answer questions that were not of clinical relevance and that is the reason for the important rate of missing values in some items of the questionnaire. Since participation in the study was voluntary, all patients were informed of the non-obligatory character of the questionnaire. Regarding glycaemic control analysis, only patients who had a recent laboratory control of HbA1c levels (during the last 12 months prior visit) were included.

A more detailed presentation has also been added in the main text (page 9, lines 8-9; page 12, line 4). 755 out of the 1141 patients who visited participating diabetes centers fulfilled this criterion. However, another 69 participants were further excluded due to being part of the recent diabetes diagnosis group.

7. The separation of treatment modalities into "oral" and injectable" is being used since the introduction of GLP-1RA based therapies. However, for the present analysis, insulin treatment should be examined separately as it is usually administered to later stages of the disease and previous research has repeatedly shown that it is associated with poorer glycemic control. Does the association of injectables with better glycemic control remain after this separation?

We would like to thank the reviewer for his very insightful comment. The authors agree that the relationship between injectable treatments and glycaemic control may be partly explained by the effect of GLP-1RA based-therapies on glycaemic control. A comment regarding this explanation has also been added in the discussion section (page 13, lines 16-20).

Moreover, since adding all available pharmaceutical schemes in the model so as to adjust for their effect on glycaemic control would result in a large number of covariates being added and a subsequent important reduction in the statistical power of the model, we only adjusted for insulin as proposed by the reviewer. Results are presented in the Table below. As can be seen no variations exist compared to our base case results, even after controlling for the effect of insulin in the model.
Table 1. Results of the multivariate logistic regression model after included insulin covariate

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Ref.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.53</td>
<td>1.05-2.22</td>
<td>0.03</td>
</tr>
<tr>
<td>Duration of T2DM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-5 years</td>
<td>Ref.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-10 years</td>
<td>1.08</td>
<td>.65-1.79</td>
<td>0.76</td>
</tr>
<tr>
<td>≥10 years</td>
<td>0.91</td>
<td>.58-1.42</td>
<td>0.68</td>
</tr>
<tr>
<td>BMI score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI&lt;25 (kg/m2)</td>
<td>Ref</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI 25-30</td>
<td>2.08</td>
<td>1.05-4.11</td>
<td>0.04</td>
</tr>
<tr>
<td>BMI &gt;30</td>
<td>2.14</td>
<td>1.12-4.08</td>
<td>0.02</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>Ref.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>1.16</td>
<td>.80-1.69</td>
<td>0.43</td>
</tr>
<tr>
<td>Age</td>
<td>1</td>
<td>.99-1.02</td>
<td>0.62</td>
</tr>
<tr>
<td>HDL levels (mg/dl)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>HDL &gt;40</td>
<td>Ref.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL ≤40</td>
<td>2.12</td>
<td>1.44-3.12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL levels (mg/dl)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>LDL&lt;100</td>
<td>Ref.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL ≥100</td>
<td>1.53</td>
<td>1.06-2.20</td>
<td>0.02</td>
</tr>
<tr>
<td>Pharmacological treatment</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Oral antidiabetic agents</td>
<td>0.92</td>
<td>.48-1.95</td>
<td>0.97</td>
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<tr>
<td>Injectable antidiabetic agents</td>
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<td></td>
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<td>On treatment with insulin regimens</td>
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<td></td>
</tr>
<tr>
<td>No</td>
<td>Ref.</td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>1.23</td>
<td>.56-2.74</td>
<td>0.61</td>
</tr>
</tbody>
</table>

8. It is a bit striking that the majority of patients followed-up by specialists are treated with monotherapy. Please comment.
A possible explanation might be the barriers in access to primary healthcare. Most of the patients who visit specialized diabetes centers, should and could easily be monitored by physicians or general practitioners and not by qualified medical personnel [4], nonetheless, they may be unable/unwilling to access or pay for one. To support this, and as previously mentioned in the literature, approximately 60% of chronically ill patients in Greece report facing significant economic limitations or extended waiting lists to access health services. As a result, during the period 2011-2013 they have reduced the number of visits to primary care services by 30% and their out of pocket health -expenditures by 20% [5].

This finding is in accordance with a previous study based on nationwide prescription data that has estimated the percentage of patients on monotherapy at approximately 42%, excluding patients treated with insulin [6].

9. The inverse association between HDL-C and HbA1c is expected due to the rise in TGs in poorly controlled patients, which in turn, are inversely correlated to HDL-C. Hence, low HDL-C in poorly controlled patients is the consequence of hyperglycemia rather than a causative factor. This should be added in the discussion. Further on, higher levels of LDL-C in poorly controlled patients should be examined in association with statin use.

Unfortunately, in the registry only data regarding anti-diabetic medications were collected. As a result, a specific analysis exploring the relationship between poor glycaemic control and statin use cannot be conducted. However, we agree with the reviewer that the associations between poor glycaemic control and lipid profile is not straightforward and we have encompassed reviewer’s comment regarding their relationship in the discussion section (page 14, lines 8-12).

10. How many patients were included in the multivariable model analysis?

591 patients were included in the multivariate model. This figure was also added to the table’s legend.

11. Page 14, lines 5-10: this is part of the results section, not the discussion.

The pertinent paragraph has been rephrased so as to achieve a connection between study results and existing literature. A part of it has been also moved to the Results section.

12. Finally, the authors should further discuss the representativeness of the study findings. Please compare to previous studies in the same country.

Results from a recent registry study in Greece were added in the main text. Moreover, a comment regarding the representativeness of study findings has been added in the limitations section of the manuscript (page 16, lines 15-17).

John Doupis (Reviewer 2):

The authors of this manuscript investigated the Profile and Factors Associated with Glycaemic Control of patients with type 2 Diabetes in Greece. They reported that poor glycaemic control was associated with inadequate lipid control, family history of diabetes and presence of obesity, while the use of injectable antidiabetic agents was associated with better glycaemic control.

1. Although the authors are stating that "This is a multi-center, non-interventional, prospective study" it seems to this reviewer that is more like an observational study. Please correct this term in the
Changes were made throughout the manuscript following reviewer’s comment.

2. "61.5% and 58.9% out of total study sample reported previous diagnosis of dyslipidemia and hypertension, respectively" Did the authors recorded the lipidemic and hypertension status only by patient self-report or did they consider also the anti-hypertensive and hypo-lipidaemic medication and Lab reports. This has to be clarified by the authors.

We would like to thank the reviewer for his valuable contribution. The authors apologize for their omission. Participants were classified as suffering from hypertension if they reported a previous diagnosis of hypertension or/and were receiving anti-hypertensive medication. Moreover, participants were classified as having dyslipidemia if their serum lipids levels were other than optimal and/or if they were on treatment with lipid lowering medications.

A more detailed clarification of classification criteria for both disorders is now added in the main text (page 9, lines 12-15).

References