Author's response to reviews

Title: Family history of diabetes and clinical characteristics in Greek subjects with type 2 diabetes

Authors:

Athanasia Papazafiropoulou (pathan@ath.forthnet.gr)
Alexios Sotiropoulos (alesot@ath.forthnet.gr)
Eystathios Skliros (eskliros@otenet.gr)
Marina Kardara (mkardara@yahoo.com)
Anthi Kokolaki (anthi_xios@yahoo.gr)
Ourania Apostolou (s.pappas@nikaia_hosp.gr)
Stavros Pappas (el.pappa@yahoo.gr)

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Title: Familial history of diabetes and clinical characteristics in Greek subjects with type 2 diabetes

Authors:

Athanasia Papazafiropoulou: pathan@ath.forthnet.gr
Alexios Sotiropoulos: alesot@ath.forthnet.gr
Eystathios Skliros: eskliros@otenet.gr
Marina Kardara: mkardara@yahoo.gr
Anthi Kokolaki: anthi_xios@yahoo.gr
Ourania Apostolou: s.pappas@nikaia_hosp.gr
Stavros Pappas: el.pappa@yahoo.gr

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The Biomed Central Editorial Team

Object: MS: 1304077578227245 - Familial history of diabetes and clinical characteristics in Greek subjects with type 2 diabetes. Dr A. Papazafiropoulou et al.

Thank you for consideration of our manuscript for publication in your journal. We have reviewed the above manuscript according to your reviewer’s comments.

Reviewer #1 (Mark McLean)

MAJOR COMPULSORY REVISIONS

1. In essence this study surveys 1473 patients with Type 2 diabetes and correlates family history of T2D with their clinical characteristics. There is now good evidence that mothers transmit diabetes to their offspring much more frequently than do fathers. This study again finds excess maternal transmission of T2D, and probably has the data to make further more novel observations. For example, whether T2D acquired through maternal transmission has different characteristics from that originating with the father. However, the research questions and hypotheses are not clear defined and some opportunity for interesting analysis might have been missed. Is this study designed to assess the effects of maternal transmission of diabetes to her offspring? If so, the experimental design should focus on that question. Or is the intention to examine a more general effect of family history (but then what is the specific hypothesis)? THE RESEARCH QUESTION AND HYPOTHESIS NEEDS TO BE MORE CLEARLY DEFINED

The research question is redefined on page 4 “The aim, therefore, of the present study was to evaluate possible differences in the prevalence of maternal and paternal history of T2D in Greek patients, and to evaluate their impact on the patient’s metabolic control and diabetic complications”. As you have mentioned there is now good evidence that mothers transmit diabetes to their offspring much more frequently than do fathers. The present study is the first one to estimate the impact of maternal transmission of type 2 diabetes in our country. Therefore, our aim was to estimate the prevalence of maternal and paternal transmission in our country.
Furthermore, we tried to reveal any differences between diabetic subjects according to the pattern of family transmission of diabetes. In the “Results” section an analysis regarding patient’s characteristics according to maternal or paternal transmission is done.

2. To my mind the most interesting question is whether a maternal diabetes history transmits T2D with different characteristics to paternal transmission – suggesting an additional maternal influence beyond simple genetics (such as an epigenetic effect of intrauterine hyperglycaemia, mitochondrial genes or maternal imprinting). Comparison with patients who have other relatives (not parents) affected is less useful. There were 277 patients with a diabetic mother and 110 with a diabetic father. There were a further 60 patients in whom both parents were diabetic and it is not clear how data was analysed from these subjects; or whether they were excluded. I would suggest that the most appropriate analysis to detect non-genetic maternal effects is to include these subjects in the “diabetic mother” group. The analysis would then be those with a diabetic mother versus those whose mother is not diabetic. This would allow best determination of any “maternal transmission” effects. THE COMPARITOR GROUPS IN THE ANALYSIS SHOULD BE MORE CAREFULLY CHOSEN TO ADDRESS THE DEFINED RESEARCH QUESTION

• Your observation is very interesting and would add more information to the manuscript. However, the method that we followed to the present study does not allow us to further evaluate an additional maternal influence such as an epigenetic effect of intrauterine hyperglycaemia, mitochondrial genes or maternal imprinting.

We found 60 patients in whom both parents were diabetic. We used this subgroup in the comparison between subjects with parents with diabetes vs. subjects with no relatives with diabetes. This is now stated on page 6 “[this subgroup was used in the comparison between subjects with parents with diabetes vs. subjects with no relatives with diabetes]".
Indeed the comparison with patients who have other relatives (not parents) with diabetes did not offer additional information to the analysis. We added a new comparison group with the title “Subjects with diabetic mother vs. subjects with relatives others than mother with diabetes” on page 8 for the best determination of any “maternal transmission” effects, as you have suggested “The comparison between diabetic subjects with mother with diabetes and diabetic subjects with relatives others than mother with diabetes showed the following differences: diabetic subjects with mother with diabetes were significantly younger (P = 0.003), had lower age at diabetes diagnosis (P < 0.001), and a lower prevalence of hypertension (P = 0.001) (Table 2). No significant differences were observed regarding gender distribution, blood pressure, HbA1c, BMI, plasma total cholesterol levels, HDL-cholesterol levels, LDL-cholesterol levels, triglycerides levels, dyslipidemia, retinopathy, nephropathy, CAD and anti-diabetic treatment”. However, the analysis between the above mentioned groups did not add more information regarding the impact of maternal transmission of diabetes.
3. Some of the outcome measures are poorly explained. What is meant by “no difference in diabetes medications”? It would be interesting to know whether patients with a maternal diabetes history required higher doses of oral medication or insulin, or were more likely to be treated with insulin. It is not clear whether this was assessed.

- It is true that in the present study we did not assess the doses of oral medication or insulin. However, the analysis of the existing data showed no differences in oral medication and insulin between the study subgroups (Tables 1-3).

4. In the discussion there are some incorrect assertions. The authors suggest that the effect of the intrauterine environment in programming diabetes in later life is predominantly via restriction of fetal growth – producing what we might now call “Barker’s syndrome” (small baby, diabetes and cardiovascular disease in adulthood). This is naïve when discussing maternal diabetes. Maternal diabetes tends to produce a macrosomic infant who later becomes diabetic. The mechanism is likely to be quite different from the situation described by Barker; possibly involving programming of beta-cell function, appetite regulation and insulin sensitivity. The discussion also refers to “paternal gene imprinting” when maternal imprinting would be the correct concept.

- The corrections have been done to the manuscript on page 9 “It is known that the intrauterine environment in mothers with diabetes during pregnancy is associated with insulin resistance and adult T2D [12, 21]”, as well as to the references. In addition the expression “paternal gene imprinting” has been corrected on page 9 “Furthermore, genetic factors, including mitochondrial inheritance [22, 10], genetic imprinting [23], and behavioural risk factors passed on preferentially by the mother [24, 25]”. 
5. Were the statistical analyses corrected for multiple comparisons (eg a Bonferoni correction)? Some of the p values close to 0.05 may lose significance if appropriate correction is made for the multiple variables.

- This is now stated in the text on page 6 “Differences between the studied groups examined using the student’s unpaired $t$-test or the Mann-Whitney $U$-test for parametric and non-parametric data, respectively, while a chi-square test was used for categorical data. Bivariate correlations were performed using the Pearson or the Spearman correlation coefficient, as appropriate”.

MINOR BUT ESSENTIAL REVISIONS

6. In the abstract “patients with parental diabetes had a higher prevalence of hypertension….. than patients with diabetes in the mother”; the underlined word should be paternal.

- The correction has been done on page 3 “Patients with paternal diabetes had a higher prevalence of hypertension”.

7. Reference 10 and reference 31 are duplicates

- The correction to the references has been done.

8. Albumin excretion rate is measured in micrograms per minute, not milligrams

- The correction has been done on page 6 “The renal status was based on the albumin excretion rate (AER) measured in at least two out of three consecutive 24-h timed urine collections. Patients were classified as normo- (AER< 20 micrograms/min), micro- (AER 20–199 micrograms/min), or macroalbuminurics (AER > 200 micrograms/min)”.
9. Page 10 “Another simply explanation…”, should be “simple explanation”

- The correction has been done on page 10.

10. Page 10 “On the contrary with a previous report…..”; would be better expressed as “In contrast with…….”

- The correction has been done on page 10.

2nd Reviewer (Samy HADJADJ)

MAJOR POINTS

1. A flow chart would strongly improve the manuscript allowing to assess patient eligibility.

- Thank you for your comment. However, a flowchart would not offer additional information to the manuscript regarding patient's eligibility. The inclusion criteria are stated clearly at the “Patients and Methods” section.

2. In addition, the paper relates to the Greek population. It should be precised if this study is population based or not (which is probably not the case).

- As you have mentioned the present study is not a population based study. As data were collected from a referral tertiary center, they cannot be extrapolated to the total population. This is now stated on “limitations” section on page 11 “As data were collected from a referral tertiary center of diabetes, they cannot be extrapolated to the total population”.
3. In the abstract there are no ways to compare different findings. Mean +/- should be added

- The corrections are now stated on “abstract” section:

page 3 “64.8 vs. 57.1%, P = 0.05”

page 3 “115.12 ± 39.76 vs. 127.13 ± 46.53 mg/dl, P = 0.006”

page 3 “31.22 ± 5.87 vs. 30.67 ± 5.35 Kg/m², P = 0.08”

page 3 “higher prevalence of dyslipidemia (49.8 vs. 44.6%, P = 0.06) and retinopathy (17.9 vs. 14.5%, P = 0.08)”

4. The limitations of the manuscript should include the fact that no all type 2 diabetes patients in this institution were recruited.

- It is stated clearly at the “Patients and Methods” section that only type 2 diabetic patients with at least three visits during the last year were enrolled into the study in order to avoid conflicting factors. This is now stated on “limitations” section on page 11 “As data were collected from a referral tertiary center of diabetes, they cannot be extrapolated to the total population. In addition, only type 2 diabetic patients with at least three visits during the last year were enrolled into the study”.

5. In the context of the possible additional benefit of genetic information, it should be noted if DNA was collected for these patients.

- We did not collect DNA samples by the patients that were enrolled to the present study. The present study is an observational one, aiming to estimate the impact of maternal or paternal transmission of type 2 diabetes in a sample of Greek diabetic patients. However, we do not find necessary to mention that in the manuscript.