Author's response to reviews

Title: Treatment outcome of patients with comorbid type 1 diabetes and eating disorders

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Version: 2
Date: 23 April 2014

Author's response to reviews: see over
Dear Prof. Fassino,

Attached please find the electronic file of the manuscript entitled “Treatment outcome of patients with comorbid type 1 diabetes and eating disorders” to be resubmitted to BMC Psychiatry.

The present version of the manuscript includes modifications in response to the concerns raised by the reviewers and some additional changes which we thought could improve the paper significantly. According to the editor’s request, all tables have been placed in the main manuscript file and the copy of additional files has been removed. For the sake of clarity and conciseness, we refer to each topic in the same order as listed by the reviewers. Please read below:

**Reviewer(s)' Comments to Author:**

**Reviewer's 1 report:** Giovanni Abbate-Daga

The manuscript considers a well-defined and relevant topic, namely features and outcome of patients with eating disorders (EDs) and comorbid type 1 diabetes (T1DM). Although this issue has been long known, in literature there is a lack of studies on this matter, particularly as regards treatment response and dropouts. Therefore, the article, in spite of the small sample size considered, seems novel and thought-provoking.

However, it can be improved as follows:

Major Compulsory Revisions

**Query 1**

Introduction
Saying that T1DM individuals are at “high risk” of developing ED seems too strong also given the sample (1.06% of total ED cases). I would suggest to remove “high”. Moreover, individuals at risk are characterized by purging rather than restricting symptomatology (see the meta-analysis conducted by Mannucci et al. 2005) and such datum should be discussed in the introduction and discussion also referring to the results since a mixed-diagnosis sample has been considered.

Reply to Query 1:
We agree with the reviewer, therefore the term "high" has been removed from the introduction. The Meta-analysis by Mannucci et al 2005, has now been commented on in the introduction (Page 4) and in the discussion section (Page 7) and it has been added into the reference list (reference number 2).

Query 2
Statistical analysis
If the reviewer is not mistaken, the authors stated to assess the correlation between personality profiles and dropout, but such data are not shown either in the results or in the discussion.

Reply to Query 2
The authors would like to apologise that within the statistics analysis section the aim of assessing the correlation between personality profiles and dropout was not removed from an earlier draft. The decision was made not to add this aim due to the small numbers of patients studied. This has now removed from the text (page 4).

Query 3
Results
The features of the sample should be better described. What was the age of diabetes onset? We know indeed that age at onset is associated with the risk of EDs (Yasuko et al. 2011).

Reply to Query 3
As requested this information has been added into the text:
“For T1DM patients, the mean age of the diabetes diagnosis was 15.1 years-old (SD=6.2, interquartile range from 10.5 to 17 years) and the mean duration of the illness was 10.3 years (SD=8.2, interquartile range from 3 to 15 years)” (Page 5).

Query 4
ED diagnostic distribution should be presented not only as a total, but also divided into ED + T1DM and ED without T1DM groups.

Reply to query 4
As both groups were matched, both groups had the same ED diagnostic distribution. Information has now been added into the text explaining this distribution: “ED diagnostic distribution was: 10.0% "AN and sub-threshold AN", 25.0% "BN and sub-threshold BN", 10% BED and 55% “Pure” EDNOS (the same distribution for the both groups, for T1DM and for No-DM as they were matched on this variable)” (page 5).

Query 5
Treatment outcome: patients with ED + T1DM showed worse outcome and were more likely to dropout. It would be interesting to show the same table divided according to diagnostic groups. I know some cells may be very small but dropout rates vary across different diagnoses.

Reply to query 5
We have included a new supplementary table with the distribution of the therapy outcomes stratified by both, the eating disorder subtype and the presence of diabetes. No statistical differences, due to ED subtype, were found for the risk of dropout or partial-total remission in the No-DM patients (p=.284 and p=.523) and the T1DM group (p=.286 and p=.523) (table S2).

Query 6
As a trivial note: the percentage of 94.74% for 18 patients out of 20 is wrong.

Reply to query 6
We apologies, this has been now corrected in the text: “T1DM used insulin manipulation to control weight as most of them (n=18, 90%)” (page 5).

Query 7
Discussion
The discussion is clear but somehow too succinct. For the sake of the diffusion of scientific knowledge, the authors should discuss the difference of ED patients with T1DM in comparison with the dia-bulimia phenomenon, highly common among adolescents with diabetes (ranging between 10 and 40%).

Moreover, the temperament trait of low persistence in those with both ED and T1DM should be discussed more: this finding could explain an instable rather than lower motivation and it can represent a relevant difference with respect to psychopathology (e.g., restricting vs purging).

As a limitation it should be highlighted that future studies need to investigate as to whether the presence of comorbid diabetes impacts motivation to treatment per se.

Reply to query 7:
Dia-bulimia: Information about Diabulimia has been added in the discussion section.
“Eating disorders, particularly Bulimia nervosa has been previous associated to T1DM (2). The association between both conditions is so clear that a new term, which is not yet a medically recognized condition, has recently been described in the literature, Diabulimia. This condition has been particularly described among the adolescent population, as weight management during this time of development for individuals with diabetes can be particularly difficult forcing them to restrict or omit insulin (15) (page 7).”

Low persistence: The discussion section has now added some information regarding the role of low persistence in relation to outcome.

“The fact that individuals with T1DM present with low persistence which is associated to low frustration tolerance and low perseverance may explain the high levels of drop outs and the poor outcomes found among these individuals (page 6”).

Future studies. As suggested by reviewer the need to study motivation in this population has been added into the discussion section:

“Although recent meta-analysis has demonstrated that T1DM are particularly associated with Bulimia Nervosa (2), this study has included all type of eating disorders, future studies may want to focus in exploring the outcome of patients with T1DM and Bulimia nervosa. Moreover, future studies may want to consider investigating whether the presence of comorbid diabetes impacts motivation to treatment per se” (page 7).

Query 8

Finally, mentioning dialectical behavioral therapy seems not very pertinent since patients with ED and T1DM showed less self-harm behaviors; the authors could more properly comment instead on the need to tailor diabetes-specific treatments in EDs as well as to inform diabetologists more.

Reply to Query 8

The mention about dialectic behavioral therapy in the discussion section ahs now been removed. Information regarding the need of modification of interventions has been added.

“And will suggest the need for interventions to be modified for this population and for dialectologists to be informed about the risk of poor outcome that patients with both conditions present” (page 6).
Reviewer's 2 report: Francesco Rotella

The authors performed a study aimed at comparing clinical, psychopathological and personality features in Eating Disorders (EDs) patients with and without comorbid type 1 diabetes mellitus (T1DM). Furthermore, authors performed an intervention of 16 sessions of cognitive-behavioral therapy (CBT) in order to evaluate differences in treatment outcome between the two groups. The topic is of great interest. However, there are some methodological issues that significantly impair the quality of the results. Furthermore, given the very low prevalence of EDs in comorbidity with type 1 diabetes, from an initial sample of 1887 patients with EDs, only 20 patients were included in the study. Therefore, the sample size is very limited and the data reported are almost anecdotal.

Major compulsory revisions

Query 9
Introduction:
The introduction appears very narrow and do not place the reader in the adequate perspective. For example, some meta-analyses have been published taking into account the association between EDs and type 1 diabetes. This association can be explained in several different ways and varies in different EDs diagnostic groups.

Reply to Query 9
The literature has been updated and the newly published meta-analysis has been added (As per Query 1 Reply).

Query 10
AN, BN and BED have been associated to different temperamental profiles (e.g. Krug I, Root T, Bulik C, Granero R, Penelo E, Jiménez-Murcia S, et al. Redefining phenotypes in eating disorders based on personality: A latent profile analysis. Psychiatry Res 2011;188:439–445). For example, the temperamental feature “Persistence” seems associated only to AN Restricting type. This information should be given and discussed.

Reply to Query 10
The above study has been added into the introduction section and the authors have summarised the study and link into to the current work.
“...current treatments for individuals with ED do not vary depending on whether the person suffers from T1DM or not, although the clinical and personality characteristics may differ. Research examining the personality characteristics and temperament profile in the field of eating disorders has identified that certain eating disorders, such as bulimia nervosa purging type, are included in the maladaptive profile, particularly related to impulsivity, which will be
associated with high dropouts. In addition restrictive symptomatology is overrepresented in the adaptive profile [6], (page 3).

Query 11
Methods, Participants:
3. Some relevant information on patients with diabetes is missing. At least duration of illness and glycemic control should have been assessed.

Reply to Query 11
As suggested the available information has been added into the text.
“For T1DM patients, the mean age of the diabetes diagnosis was 15.1 years-old (SD=6.2, interquartile range from 10.5 to 17 years) and the mean duration of the illness was 10.3 years (SD=8.2, interquartile range from 3 to 15 years). In this group of patients, mean HbA1c was 9.94 % (SD=3.00) (normal range 4.5-6%) at baseline” (page 5).

Query 12
The fact that the samples are composed of patients with different EDs psychopathology (i.e. AN, BN, BED and EDNOS), can have significantly affected the results.

Reply to Query 12
We agree with the reviewer, but for this reason the T1DM patients were matched for diagnosis subtype and age of onset.

Query 13
Results:
Almost all T1DM patients used insulin manipulation to control weight. This data should be discussed, especially when reporting that no difference was found between groups for compensatory behaviors.

Reply to Query 13
This finding has been added into the result section more clearly and has been briefly discussed in the discussion section:

“Except for insulin misuse, there were no statistical differences between the two clinical groups for any other eating disorder related behaviour and psychopathology” (page 5).

“The lack of difference in purging behavior and the differences in self-harm and suicidal behaviour between the two groups may point towards the importance of analyzing the role of insulin misuse in this population” (page 7).
**Query 14**

Results, Treatment outcome:
6. The distribution of dropout rates for T1DM patients reported in the text is not clear. Numbers of patients and the distribution for patients without T1DM should be included. Furthermore, this distribution seems slightly different from what shown in Figure 1.

**Reply to Query 14**

As per reviewer 1 a new supplementary Table (Table S2) has been added to make this finding clearer. It shows the complete distribution (observed frequencies -count- and percentages) of the therapy outcomes stratified by the Eating Disorder subtype and the presence-absence of diabetes. Additionally, Table S3 includes the count with the percentage of the outcomes. Furthermore, the data represented in the Figure 1 are consistent with the values given in the text and in the Table S3. It should be noted that Figure 1 represents the “time of survival”, that is, the time until the dropout event occurs. For a risk of, for example, 25% of drop-out, 75% of patients “survive” without dropout at the end of the follow-up.

**Query 15**

Discussion:
The Discussion is also narrow. The fact that T1DM patients display lower “Perceived intensity of ED” and lower “Impairment” scores may explain higher dropout rates. It may be hypothesized that T1DM do not recognize the need for a treatment for the ED.

**Reply to Query 15**

The discussion section has been modified substantially based on reviewer 1 comments. Information regarding the role of low perceived intensity of ED has been added into it.

“The lack of motivation for change found among individuals with T1DM may also be a reflection of the low levels of consciousness regarding the illness, the low perceived intensity and low perceived impairment which suggests the importance of working with Motivational Enhancement intervention when working with individuals with T1DM and ED” (page 7).

**Query 16**

Minor essential revisions

Abstract:
The conclusions are in line with the results reported by authors.

**Reply to query 16**

The results section of the abstract has been modified accordingly.

**Query 17**
Methods, Participants:
The 55% of the patient have a diagnosis of EDNOS. The subtype (A or B) should be addressed as the two different subgroups display different psychopathological features.

Reply to Query 17
This information has now been added into the text.

“In order to aid the interpretation of the results and make it relevant to the current DSM-5 diagnosis, the EDNOS category will be divided into patients with sub-threshold AN (who fulfil the diagnosis of DSM-5 of AN under the current diagnostic criteria), patients with sub-threshold BN (who fulfil the diagnosis of DSM-5 of BN under the current diagnostic criteria) and patients with “Pure” EDNOS” (page 4).

Query 18
Figure 1:
“Time” variable is not clear. It should refer to the number of CBT session, but, if this is the case it is not clear why values >16 are included in the figure.

Reply to query 18
This Figure 1 has now been reviewed and altered in order to limit the values of the X-axis from 1 to 16.
Reviewer’s 3 report: Carla Maria Gramaglia

The issue discussed by the Authors is of interest for those working in the field. The Authors themselves underscore that in 13 years they were able to identify only 20 subjects with comorbid T1DM and ED, out of a sample of 1887 patients. Anyway, a deeper understanding of the possible psychopathological and outcome differences between ED and ED+T1DM may be helpful in planning treatment interventions.

Query 19
Some suggestions for minor revisions:
Check the manuscript for typing errors (e.g. Background section, missing full stop after [2,3]; Results section, third paragraph, missing bracket (less self-perceived intensity of the ED and less perceived impairment.).

Reply to query 19
As suggested by the reviewer, these aspects have been corrected.

Query 20

Reply to Query 20
According to the comments of the reviewer, these aspects have been included in the manuscript.

“The study is limited by sample size, the patient’s reliability about self-reporting insulin under-dosing and the possible influence of T1DM on ED questionnaires [16] (page 8)”.

Query 21
In the discussion, please expand on the differences in self-harm and suicidal behaviours between the two groups.

Reply to Query 21
As suggested by the review further information in the discussion section has been added.
“For example, the lower number of self-harm behaviours in patients with T1DM may indicate that patients with this condition may not require the use of self-harm in order to deal with emotions as they may use insulin misuse instead. It can be hypothesized that insulin abuse, which leads to weight loss, is more closely connected to mood regulation and self-harm behaviour than to weight and shape issues, although this will need to be researched further” (page 7).

We are very grateful for the reviewer’s comments as we strongly believe they have led us to considerably improve the manuscript.

Yours sincerely on behalf of the authors,

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