Author’s response to reviews

Title: Depression differed by midnight cortisol secretion, alexithymia and anxiety between diabetes types: a cross sectional comparison

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Author’s response to reviews:

To BMC Psychiatry

Dear Mario Juruena, Associate Editor of BMC Psychiatry,

We hereby resubmit the manuscript which is now titled: Depression differed by midnight cortisol secretion, alexithymia and anxiety between diabetes types: a cross sectional comparison by authors Eva O Melin, Maria Thunander, Mona Landin-Olsson, Magnus Hillman, Hans O Thulesius, to be reconsidered for publication as an original research article in BMC Psychiatry.

Point by point answers to reviewers

Thank you for your valuable comments on our manuscript. We have now answered to your comments point by point as follows:
Reviewer reports:

Reviewer 1: * Atypical depression versus melancholia in diabetes in a cross sectional comparison - depression differs between diabetes types by midnight cortisol secretion, alexithymia and anxiety

Answer: We have changed the title according to your suggestion: Depression differed by midnight cortisol secretion, alexithymia and anxiety between diabetes types: a cross sectional comparison. (Title page, lines 1-2, Page 1)

Running head: Depression, diabetes and midnight cortisol

Answer: We have changed the running head according to your suggestion. Atypical depression, melancholia, diabetes and midnight cortisol. (Title page, line 3, Page 1).

* Keywords: alexithymia, anxiety, atypical depression, cortisol, diabetes mellitus, melancholia, obesity.

Answer: We have changed the key words according to your suggestion: Alexithymia, anxiety, depression, cortisol, diabetes mellitus (After the abstract, line 59-60, Page 3)

* Persons with type 2 diabetes (T2D) or type 1 diabetes (T1D) have an increased prevalence of depression [1,2], higher in T2D than in T1D [3].

Answer: The prevalence of depression in diabetes is increased [1–3], in type 2 diabetes (T2D) 19-25% [1,2], in type 1 diabetes (T1D) 12-19% [2,3], which could be compared to a prevalence of around 11% in a non-diabetic population [2]. (Background, lines 79-81, p 4).
Melancholia and atypical depression are two subtypes of depression [7].

Add definitions of the two subtypes on DSM/ICD

Answer: We have made several changes to answer this comment and to comments given by other reviewers. We have rewritten the introduction and changed in the methods section:

The main features of depression are dysphoria, anhedonia and lack of interest, which are accompanied by features such as weight changes, sleep disturbances, psychomotor agitation or retardation, lack of energy and/or cognitive deficits [4]. Melancholia and atypical depression are two subtypes of depression [4,5]. In melancholia, there is an activation of the corticotropin releasing hormone (CRH) system including the hypothalamic-pituitary-adrenal (HPA) axis with increased cortisol secretion, the locus coeruleus, and the sympathetic nervous system [5]. Melancholia is accompanied by anxiety, a readiness to negatively charged memories, and is characterized by hyper-arousal, insomnia, loss of appetite, and weight loss. In atypical depression, there is CRH deficiency with a down-regulation of the HPA axis with decreased cortisol secretion, and a decreased sympathetic activity [5]. Atypical depression is generally not accompanied by anxiety, but is associated with a sense of emptiness, and persons with atypical depression seem to be “walled off”. The clinical picture is characterized by hypo-arousal, inactivity, hypersomnia, hyperphagia, and weight gain [5]. (Background, lines 63-76, p 4).

A new section under a new heading is added:

Clinical psychiatric diagnoses

Classification numbers for both melancholia and atypical depression are as follows: DSM-IV/ICD-10: single episode 296.2/F32 or as recurrent episodes 296.3/F33 [4]. No clinical differentiation was performed between depression types. Clinical psychiatric diagnoses were dichotomized as having or not having a psychiatric diagnosis. (Methods, lines 146-150, p 7).

Even mild increase in cortisol secretion in a non-diabetic population without clinical signs of overt hypercortisolism, is associated with an increased risk of cardiovascular events and mortality [14].

Answer: We have performed the correction. (Background, line 97-100, p 5).

One hospital diabetes outpatient clinic in southern Sweden
Answer: the diabetes outpatient clinic of the Central Hospital in Växjö, Sweden. (Methods, lines 124-125, p 6).

* Data were collected from the Swedish National Diabetes Register and from computerized medical records.

Data were gathered from the Swedish National Diabetes Register and from computerized medical records.

Answer: We have performed the change. (Methods, line 143, p 7).

Reviewer 2: Paper topic is important.

"The main hypothesis was that persons with T2D predominantly suffer from symptoms of atypical depression, and persons with T1D predominantly suffer from symptoms of melancholia. The primary aim of this work was to compare the two diabetes types regarding depression type and midnight salivary cortisol (MSC) secretion."

It is important and significant in distinguishing types of depression and correlating them with types of diabetes.

I would recommend citation of either World Health Organization biosocial criteria for depression or biomedical criteria for the DSM V on Depression.

Answer: We have cited DSM-IV and given the numbers for the diagnoses. We write:

The main features of depression are dysphoria, anhedonia and lack of interest, which are accompanied by features such as weight changes, sleep disturbances, psychomotor agitation or retardation, lack of energy and/or cognitive deficits [4]. Melancholia and atypical depression are two subtypes of depression [4,5]. (Background, lines 63-66, p 4).

Clinical psychiatric diagnoses

Classification numbers for both melancholia and atypical depression are as follows: single episode 296.2/F32 or as recurrent episodes 296.3/F33 [4]. No clinical differentiation was performed between depression types. Clinical psychiatric diagnoses were dichotomized as having or not having a clinical psychiatric diagnosis as in our previous studies [6,7]. (Methods, lines 145-149, p 7).
Reviewer 3: Thank you for giving me the opportunity to read the manuscript entitled "Atypical depression versus melancholia in diabetes in a cross sectional comparison - depression differs between diabetes types by midnight cortisol secretion, alexithymia and anxiety". Though the methods described are sound, I feel the manuscript could be improved in a number of ways. I first give general comments, and then provide more detailed feedback for each section.

General comments:

- The title is too long, and is actually misleading: 1) it is not depression that is investigated in this research study, but rather depressive symptoms, as a screening tool is used, not a diagnostic assessment;

2) Similarly, it is participants' clinical characteristics that are measured, not atypical depression or melancholia per se - the fact that characteristics differ between the two diabetes types, suggesting different subtypes of depression, is a finding of the paper, not the main research question.

Answer: We have changed and shortened the title as proposed by reviewer 1:

Depression differed by midnight cortisol secretion, alexithymia and anxiety between diabetes types: a cross sectional comparison. (Title page, lines 1-2, Page 1)

We know there is a difference between a clinical diagnosis and a test result from a self-report instrument. In our first article (Melin et al., 2013) and in my thesis (2014) [8] we/I checked the associations between clinical psychiatric diagnoses and HADS-D, HADS-A and the use of antidepressants, and the associations were highly significant. To clarify the difference between clinical and self-reported depression and clinical and self-reported anxiety we have made several changes in this manuscript. We have introduced a new heading and section:

Clinical psychiatric diagnoses

Classification numbers for both melancholia and atypical depression are as follows: single episode 296.2/F32 or as recurrent episodes 296.3/F33 [4]. No clinical differentiation was performed between depression types. Clinical psychiatric diagnoses were dichotomized as having or not having a clinical psychiatric diagnosis. (Methods, lines 145-149 p 7)

Under a new heading, we write:
Self-report instruments

Self-reported depression and anxiety were assessed by the Hospital Anxiety and Depression Scale (HADS) [2,9,10]. (Methods, lines 158-160, p 7).

In the T2D patients, the associations between clinical psychiatric diagnoses were for self-reported depression crude odds ratio (COR) confidence interval (CI) 5.3 (0.5-54.0), P = 0.16; for the use of antidepressants P ≥0.99; for self-reported anxiety 2.2 (0.2-19.3), P = 0.49. The associations were previously reported for the whole population of T1D patients (n = 292) [6,28], and were between clinical psychiatric diagnoses and self-reported depression COR 10.8 (4.7-24.8), P <0.001; the use of antidepressants COR 9.6 (3.7-24.6), P <0.001; and self-reported anxiety COR 3.2 (1.6-6.3), P = 0.001. When the results are presented and discussed we use the term depression for self-reported depression and the term anxiety for self-reported anxiety. (Methods, lines 162-171, p 8).

We have changed the description of the aim:

The aim of this study was to compare between T1D and T2D the associations between self-reported depression, self-reported anxiety and alexithymia, MSC, and obesity (Background, lines 108-109, p 5).

We present the number of patients with clinical depression and clinical anxiety and write:

The prevalence of clinical psychiatric diagnoses did not differ between diabetes types (P = 0.54), the prevalence was in T2D patients 17% (clinical depression: n = 1, alcohol addiction under control: n = 1, stress related disorders: n = 2) and in T1D patients 14% (clinical depression: n = 13; clinical anxiety: n = 2; stress related disorders: n = 5). (Results, lines 217-222, p 10).

In the discussion section, we repeat the information that we study self-reported depression:

In this comparative study of self-reported depression and associated features in 24 patients with T2D and 148 patients with T1D at one hospital diabetes outpatient clinic, the depression prevalence was 25% in the T2D patients and 12% in the T1D patients. (Discussion, lines 249-251, p 11).

We also add:

Another limitation is that depression and anxiety were self-reported and not confirmed by a diagnostic interview, but the associations between clinical psychiatric diagnoses and self-
reported depression, self-reported anxiety and the use of antidepressants were previously tried and found highly significant in the T1D patients [6,8]. (Discussion, lines 270-274, p 12).

- I feel the rationale for the study is missing. The authors describe the differences between melancholia and atypical depression well, and the effects of depression on the prognosis of individuals with diabetes, but it is less clear why authors choose to investigate both depression and MSC among that population. Am I right in thinking that one type of depression is more likely to lead to increased cortisol secretion?

Answer: According to Gold and Chrousos [5] melancholia is associated with increased cortisol secretion and atypical depression is associated with decreased cortisol secretion. We have added information regarding the increased cortisol secretion and write as follows:

In melancholia, there is an activation of the corticotropin releasing hormone (CRH) system including the hypothalamic-pituitary-adrenal (HPA) axis with increased cortisol secretion, the locus ceruleus, and the sympathetic nervous system [5]. (Background, lines 66-69, p 4).

In atypical depression, there is CRH deficiency with a down-regulation of the HPA axis with decreased cortisol secretion, and a decreased sympathetic activity [5]. (Background, line 71-73, p 4).

We have also added more information about the differences between diabetes types and write as follows:

The cause of T1D is an insulin secretion deficiency due to autoimmune destruction of the pancreatic beta-cells [11]. It has been suggested that psychological stress, mediated by excess cortisol and catecholamine secretion [12], could lead to the development of autoimmunity and the induction of T1D [13,14]. Several biological links have been suggested between T1D and depression, one link is hyperactivity of the HPA axis which is present in both T1D and depressive states [15]. Type 2 diabetes (T2D) is characterized by insulin resistance and an inadequate compensatory insulin secretory response [11]. Obesity, which has a prevalence of around 10-15% in the Swedish population [16], is one risk factor for the development of insulin resistance and T2D [11,17]. Depression is another risk factor for the development of T2D [1]. However, the association between T2D and depression is bidirectional, as manifest T2D also increases the risk for the development of depression [1]. (Background, lines 84-95, p 4-5).

Which in turn may worsen prognosis of diabetes? If this is the case, then this really needs to be foregrounded in the introduction.
Answer: Increased secretion of cortisol is worsening the prognosis of diabetes.

We write in the ms:

Increased cortisol secretion is associated with increased prevalence of diabetes complications including cognitive decline and ischemic heart disease [18–20]. Even mild increase in cortisol secretion in a non-diabetic population without clinical signs of overt hypercortisolism, is associated with an increased risk of cardiovascular events and mortality [21]. (Background, lines 96-100, p 5).

Authors also briefly mention in the conclusion why understanding the different clinical presentation of depression among the two types of diabetes may be beneficial for treatment, but this should already appear in the introduction, to support the need for this research.

Answer: We have made several changes throughout the manuscript in order to explain why it is important to differentiate between depression types.

We have written under the description of atypical depression:

It is possible that it is clinically more difficult to recognize atypical depression due to the absence of anxiety and negatively charged memories. (Background, lines 76-78, p 4).

For depressed patients with alexithymia, the reduced capacity of communicating feelings might lead to an increased risk to suffer from a depressive disorder that will not be diagnosed and thus not treated. (Background, lines 105-107, p 5).

To be able to differentiate between melancholia and atypical depression might have clinical implications as the two depression types might benefit from different treatment strategies. (Background, lines 115-117, p 6).

Alexithymia might be the reason for the feelings of emptiness, and the “walled off” impression on other people that are clinical features of atypical depression [5]. The low emotional awareness and the reduced capacity of communicating feelings, features of alexithymia [22], have clinical implications. First, there is a risk that depression in persons with alexithymia will remain undiagnosed as alexithymic persons have difficulties recognizing and communicating their own feelings, thus also their depressive state. Second, alexithymic persons might benefit from different types of psychotherapy than non-alexithymic persons. (discussion, lines 285-293, p 13).

There are several subjects for future research. Do physicians fail to recognize depression in persons with alexithymia? Are the features of atypical depression, hypo-arousal, inactivity, hyperphagia and weight gain, misinterpreted clinically as just laziness or non-adherence to diabetes regiment in T2D patients? Do the two depression types benefit from different antidepressants and psychotherapeutic interventions? Cognitive behavioural therapy is
commonly used for the treatment of both depression and anxiety [23]. In future research we suggest trying whether psychotherapeutic methods aiming at increased emotional awareness and expressiveness [9,24–26] are preferable for depressed persons with alexithymia. Increased emotional awareness may be of major importance as alexithymia previously has been linked to increased cardiovascular mortality [27]. For depressed persons with increased cortisol secretion, stress reducing techniques could be tried [24,28]. (discussion, 295-309, p 13-14).

While I understand why it is important to be able to distinguish depression types among individuals with diabetes, it is still unclear why authors hypothesise that depression types would differ between individuals with type 1 and type 2 diabetes.

Answer: We have added the following information and we write:

As atypical depression is characterized by hyperphagia and weight gain [5], and obesity is associated with the development of T2D [17], we hypothesized that T2D patients suffer mainly from atypical depression. As hyperactivity of the HPA axis is suggested to be a biological link between T1D and depression [12,15], and as we previously found increased MSC in depressed T1D patients we hypothesize that T1D patients mainly suffer from depression with melancholic features [7]. To be able to differentiate between melancholia and atypical depression might have clinical implications as the two depression types might benefit from different treatment strategies. (Background, lines 109-117, p 6).

- I fear the sample of participants with type 2 diabetes is too small; the small sample is mentioned in the limitation section of the manuscript, but even if non-parametric analyses are used I feel authors should be more cautious when interpreting the results of the study.

Answer: We have written:

The main limitation of our study was the small number of patients with T2D. It will be necessary to explore whether our findings of the very strong association between depression and alexithymia, and the absence of associations between anxiety, high MSC and depression in T2D can be confirmed in a larger population. The prevalence of high MSC was non-significantly lower in the depressed than in the non-depressed T2D patients, whether this is a type 2 error is another subject for further exploration. A larger study of depression, alexithymia, anxiety and MSC in persons with T2D is therefore planned in primary care settings [24]. (Discussion, lines 263-270, p 12).
- The scale used to assess depressive and anxiety symptoms is a screening tool, and authors should be wary of using the terms depression and anxiety for those who screen above the cut-off.

Answer: We have tried to clarify throughout the manuscript the distinction between self-reported depression and anxiety and clinically diagnosed psychiatric diagnoses. See above.

Also, it may be worth explaining in the methods that the type of depression/depressive symptoms presented by participants isn't measured by this screening tool, but by assessing alexithymia, anthropometrics etc.

We write: Depression subtype was determined by the links between self-reported depression and self-reported anxiety and alexithymia, high MSC and obesity. (Methods, 137-139, p 7).

Specific comments

Abstract:

- The background section of the abstract suggests that the type of depression reported by patients with type 1 and type 2 diabetes are being compared; but actually, the study focuses on comparing the characteristics of individuals with type 1 or type 2 diabetes, with and without symptoms of depression.

Answer: We have changed the Background section and write: The aim was to compare between T1D and T2D the associations between self-reported depression, self-reported anxiety and alexithymia, MSC, and obesity. (Abstract, background, 28-30, p 2).

- Line 39-54: The way the results are reported is very confusing, especially the sentence "the prevalence rates were for depressed/non-depressed persons: high MSC T2D 17%/44% etc." (line 46-51).

I realise there are many results to report, but perhaps authors should use full sentences and reduce the number of results if they are limited by the word count.

Answer: We have changed the result section in the abstract and write as follows:

Comparisons of prevalence between diabetes types showed for T2D/T1D: depression 25%/12% (P = 0.10); high MSC (≥9.3 nmol/L) 38%/22% (P = 0.13); alexithymia 25%/13% (P = 0.12); anxiety 38%/35% (P = 0.82). The prevalence of high MSC did not differ between depressed (17%) and non-depressed (44%) T2D patients (P = 0.35), but differed between depressed (53%)
and non-depressed (18%) T1D patients (P = 0.003). The alexithymia prevalence differed between depressed (67%) and non-depressed (11%) T2D patients (P = 0.018), and between depressed (47%) and non-depressed (11%) T1D patients (P <0.001). The anxiety prevalence did not differ between depressed (67%) and non-depressed (28%) T2D patients (P = 0.15), but differed between depressed (76%) and non-depressed T1D patients (30%) (P <0.001). The obesity prevalence (BMI ≥30 kg/m2) was for the depressed patients: T2D 80% and T1D 6%. In the T2D patients, depression was associated with alexithymia (AOR 15.0). In the T1D patients, depression was associated with anxiety (AOR 11.0), foot complications (AOR 8.5), HbA1C >70 mmol/mol (AOR 6.4), and high MSC (≥9.3 nmol/L) (AOR 4.8). (Abstract, lines 37-52, p 2-3).

Background:

- P 5 lines 11-19: I would switch the two sentences around - first explain what the aim of the study is, and then what you hypothesise. Also, why is this hypothesised? What evidence is there to suggest that the two types of diabetes may be associated with different types of depression? This isn't clear from the literature reviewed in this section.

Answer: We have switched so first we explain the aim and then we hypothesize

In the article we have written:

The aim was to compare between T1D and T2D patients the associations between self-reported depression, self-reported anxiety and alexithymia, MSC, and obesity. As atypical depression is characterized by hyperphagia and weight gain [5], and obesity is associated with the development of T2D [17], we hypothesize that T2D patients suffer mainly from atypical depression. As hyperactivity of the HPA axis is suggested to be a biological link between T1D and depression [12,15], and as we previously found increased MSC in depressed T1D patients we hypothesize that T1D patients mainly suffer from depression with melancholic features [7]. To be able to differentiate between melancholia and atypical depression might have clinical implications as the two depression types might benefit from different treatment strategies. (Background, lines 108-117, 5-6).

We also, as previously described above, made several changes in the Background section where we have further described the differences in aetiology and clinical features between diabetes types. We also write in the discussion section:

We have not found any study where melancholia and atypical depression were compared between diabetes types. (Discussion, lines 281-282, p 13).
Method:

- Were all eligible patients systematically approached to take part in the study? Who approached them? Why were they sometimes recruited by the physicians and sometimes the nurses (p5 line 31)? This has an impact on the generalisability of the authors' findings, especially given the small sample recruited.

Answer:

All eligible patients were approached and the patients were consecutively recruited. We have added a figure to show the enrolment process. (Figure 1).

We have written: The participants were consecutively enrolled during a period of 9 months from March to December 2009 by specialist diabetes physicians or specialist nurses from the diabetes outpatient clinic of the Central Hospital in Växjö, Sweden. The patients consult both their physicians and nurses once a year, optionally 6 months in between. The enrolment process is described in Fig.1 (Methods, 122-127, p 6).

- P5 line 58-P6 line 6 - I would merge this information within the different subparagraphs on the different measures captured. How recent was the data collected from the medical records?

Answer: We have merged information within subparagraphs and we have introduced a new subheading:

Data collection

Data were gathered from the Swedish National Diabetes Register and from computerized medical records. Data collection was terminated in January 2010. (Methods, lines 142-144, p 7).

We have also in order to improve the methods section introduced a few more subheadings:

1) Clinical psychiatric diagnoses, see above.

2) Diabetes complications

Cardiovascular complications were defined as ischemic heart disease, stroke or transient ischemic attack. Diabetes retinopathy was defined as having non-proliferative or proliferative retinopathy, meaning microangiopathy changes as viewed by fundus photography through a dilated pupil. Foot complications were defined as significant neuropathy, angiopathy, earlier or present diabetes foot ulcer, foot infection, foot deformity, arthropathy or amputation of the lower
limb. All three complications were dichotomized as having or not having the complication. (Methods, lines 150-157, p 7).

We have changed the names of two subheadings: From Psychological variables to Self-report instruments. (Method, line 158, p 7). From Metabolic variables and hypoglycemia to Glycemic control and obesity (Method, line 196, p 9).

- P6 line 31-33: Authors should specify what a cut-off of 61 or above on that scale indicates
Answer: Alexithymia was defined as TAS-20 ≥ 61 points [29,30]. (Methods, lines 173-174, p 8).

- P7 line 45-55: Authors should be a bit more specific regarding the outcome variable that they are investigating when they are using non-parametric tests - are these tests used to compare measures between the two types of diabetes? To compare participants with vs. without depressive symptoms? Is this done separately for type 1 and type 2 diabetes?
Answer: We have performed several changes in the result section to clarify these questions:

Baseline characteristics and differences between diabetes types are presented in Table 1. The T2D patients differed from the T1D patients by higher MSC levels (P = 0.006), higher prevalence of obesity (P < 0.001) and of cardio vascular complications (P = 0.049), lower prevalence of diabetes retinopathy (P = 0.039), and shorter diabetes duration (P < 0.001).

Differences between depressed and non-depressed patients are presented separately for each diabetes type in Table 2. The depressed T2D patients compared to the non-depressed had higher prevalence of alexithymia (67% versus 11%, P = 0.018), and their BMI was non-significantly higher (P = 0.072). The depressed T1D patients compared to the non-depressed had higher prevalence of alexithymia (47% versus 8%, P = < 0.001), anxiety (76% versus 30%, P = < 0.001), high MSC (53% versus 18%, P = 0.003), and their BMI was non-significantly lower (P = 0.062). The highest prevalence of obesity was found in the depressed T2D patients (83%) and the lowest in the depressed T1D patients (6%).

For the T1D patients, the MSC levels were highest when collected in spring, intermediate in summer, and lowest when collected in autumn/early winter (P < 0.001). There was no seasonal variation of MSC observed in the T2D patients (P = 0.55).

Associations with depression are presented in Table 3 for each diabetes type separately. In the T2D patients, self-reported depression was associated with alexithymia (AOR 15.0). In the T1D
patients, self-reported depression was associated with anxiety (AOR 11.0), foot complications (AOR 8.5), high HbA1C (AOR 6.4), and high MSC (≥9.3 nmol/L) (AOR 4.8). (Results, lines 223-244, p 10-11).

Median MSC did not differ between users and non-users of inhaled steroids (T2D: P = 0.94; T1D: P = 0.58). There were no gender differences in high MSC prevalence (T2D: P > 0.99; T1D: P = 0.56). (Results, lines 245-247, p 11).

- P8 line 24: Given that individuals with severe mental disorders were excluded from the study, it would be worth explaining which 'clinical psychiatric diagnoses' are referred to here

Answer: We write: The prevalence of clinical psychiatric diagnoses did not differ between diabetes types (P = 0.54), the prevalence was in the T2D patients 17% (clinical depression: n = 1, alcohol addiction under control: n = 1, stress related disorders: n = 2) and in the T1D patients 14% (clinical depression: n = 13; clinical anxiety syndrome: n = 2; stress related disorders: n = 5). (Results, lines 217-222, p 10).

- P8 line 38-41: Another example where full sentences should be used to report results - the sentence is confusing as it stands.

Answer: See above.

- I would forego table 2 - I don't see the benefit of running non-parametric analyses, if the crude and adjusted ORs are then presented using a logistic regression (table 3).

Answer: We would prefer to keep table 2 for several reasons. For example, there are very few studies of alexithymia in Sweden. The alexithymia prevalence is not known in the general population, and the alexithymia prevalence for depressed and non-depressed, T1D and T2D patients are definitely not known before we started studying this subject. To have prevalence data published can be of value both for other researchers, and for our own future research when we want to make comparisons, both for our planned study of T2D in primary care and at follow up of our RCT. Midnight salivary cortisol samples have not been used much in research, so there are very little data published regarding ranges in different populations. We also think it is interesting to present BMI and the obesity prevalence both for the depressed and non-depressed patients.
- P9 line 4-6: I understand what the authors mean here, but it sounds like MSC levels were collected over a period of time, which isn't the case. Perhaps change the wording to "MSC levels were highest when collected in spring" etc.

Answer: We have changed this. See above.

Discussion:

- Though the authors understandably highlight the main findings of the study, it would be worth reporting the prevalence of depressive symptoms among the sample of type 1 and type 2 diabetes first.

Answer: In this comparative study of self-reported depression and associated features in 24 patients with T2D and 148 patients with T1D at one hospital diabetes outpatient clinic, the depression prevalence was 25% in the T2D and 12% in the T1D patients. (Discussion, lines 249-251, p 11).

We have also added:

The prevalence of depression for the T2D patients was the same as previously presented by Semenkovich et al. [1], and for the T1D patients the same as presented by Barnard et al. [3]. (Discussion, lines 275-277, p 12).

- P10 line 4-9: The sentence "To distinguish between depression types..." seems out of place, and would be of better use in the introduction/conclusion. Also, melancholia and atypical depression are categorised as different subtypes of depression because they present with different clinical characteristics; saying that it is important to be able to distinguish between these two types of depression is important because they differ in clinical expression is a circle argument!

Answer: We have excluded that sentence.

- It would good if authors spent more time discussing why individuals with type 1 or type 2 diabetes present with different types of depression. Also, what are the implications of these findings on the treatment of diabetes and depression?

As previously described, atypical depression is generally not accompanied by anxiety, but is characterized by a down regulation of the HPA axis, hypo-arousal, weight gain during depressive...
episodes, and a sense of emptiness [5]. Alexithymia might be the reason for the feelings of emptiness, and the “walled off” impression on other people that are clinical features of atypical depression [5]. The low emotional awareness and the reduced capacity of communicating feelings, features of alexithymia [22], have clinical implications. First, there is a risk that depression in persons with alexithymia will remain undiagnosed as alexithymic persons have difficulties recognizing and communicating their own feelings, thus also their depressive state. Second, alexithymic persons might benefit from different types of psychotherapy than non-alexithymic persons.

There are several subjects for future research. Do physicians fail to recognize depression in persons with alexithymia? Are the features of atypical depression, hypo-arousal, inactivity, hyperphagia and weight gain, misinterpreted clinically as just laziness or non-adherence to diabetes regiment? Do the two depression types benefit from different antidepressants and psychotherapeutic interventions? Cognitive behavioural therapy is commonly used for the treatment of both depression and anxiety [23]. In future research we suggest trying whether psychotherapeutic methods aiming at increased emotional awareness and expressiveness [9,24–26] are preferable for depressed persons with alexithymia. Increased emotional awareness may be of major importance as alexithymia previously has been linked to increased cardiovascular mortality [27]. For depressed persons with increased cortisol secretion, stress reducing techniques could be tried [24,28]. (Discussion, lines 283-305, p 13-14).

Table 2: I would include all the information in the footnote in the main method section of the manuscript.

Answer: We have done so except for the following: Data are n (%) or median (q1, q3). 1Fisher’s exact test unless otherwise specified. 2Mann - Whitney U test.

Table 3:

- The number of participants with type 2 and type 1 diabetes is different than in the previous tables - why is that?

Answer: There are missing values, presented in the footnote under Table 1. Altogether in the multiple regression analyses were 23 persons with T2D and 141 persons with T1D included in the multiple regression analysis. We write in the footnote:

1Multiple regression analysis (Backward: Wald): T2D: n = 23; Hosmer and Lemeshow test 0.875; Nagelkerke R2 Square 0.358. 2Multiple regression analysis (Backward: Wald): T1D: n = 141; Hosmer and Lemeshow test 0.571; Nagelkerke R2 Square 0.465.
- Change 'P' to 'P-value' to stay consistent, under Type 1 diabetes
  We have done so.

Typos:
- P4 line 55 - there is an extra comma
  Answer: We have performed the correction.
- Page 5 line 31: spell out the dates - from March to December 2009.
  Answer: We have done so.
- P5 line 58 - typo in the word 'described'
  Answer: We have done so.
- P8 line 19 - T1D, not TID
  Answer: I do not understand this.
- P8 line 36 - include 'individuals' or 'participants' after 'Depressed and non-depressed'
  We have included depressed and non-depressed patients.

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We have answered:

The data set analysed during the current study is not available publicly as individual privacy could be compromised, and we have no permission from the Regional Ethical Board to share the research data publicly. The data set is available from the corresponding author on reasonable request.